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MEDICINE MONOGRAPHS

VOLUME III

EDEMA

BY

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BALTIMORE

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PREFACE

In this monograph we have attempted to present as a connected whole the factors which regulate the water and salt content and maintain the homoiohydria and homoiotonia of the organism and its constituent parts, and edema as due to a defect in one or another part of this mechanism. In particular it is shown that such a defect may lead to a reversal in the direction of the main currents of fluid within the body.

Just as a multiplicity of physical and chemical factors is instrumental in maintaining this mechanism which regulates the distribution and movements of the body fluid, so a multiplicity of physical and chemical alterations may lead to the production of edema.

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EDEMA

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I. INTRODUCTION

Edema is a pathological condition in which fluid accumulates excessively in tissues or cavities of the body. It is due to an interference with the mechanism which regulates the water content of the body fluids and tissues, and which tends to keep it constant within certain limits and to correlate it with the salt content in such a way that the osmotic pressure likewise remains approximately constant. A series of processes participates in the maintenance of the water and salt level and it appears probable that these processes are, to a certain extent, correlated with each other in such a way that one regulatory mechanism results, comparable to the mechanism which regulates the constancy of the hydrogen ion concentration in the body fluids.

Water and salt are taken in essentially through the gastro-intestinal canal; both are absorbed and enter the blood. Through the heart action, aided by vasomotor mechanisms, the water and salts are distributed by way of the capillaries among the various tissues. Some of the fluid leaves the blood through the capillaries and thus reaches the constituents of the tissues proper. Metabolic products of the tissues are mixed with this blood transudate. Both combined constitute the interstitial fluid. A part of this is reabsorbed through the blood-vessels, another part enters, through the endothelium of the lymph vessels, into the lymphatic system and thus becomes lymph, which ultimately is again carried to the blood stream. Related to the interstitial fluid is the fluid which is found in the serous cavities, although this is apparently modified through the influence of the membrane lining these cavities.

The constant intake of water is compensated for by a continuous elimination of water through the kidney, skin and lung. We know that the intensity of elimination is regulated by the intensity of water drinking, and that the intensity of water drinking depends, to a certain extent, upon the intensity of water elimination. We know furthermore that there exists between the various mechanisms which take care of the water elimination, a correlation of such a nature that diminished activity of one organ is compensated for by an excess activity of another organ.

There is in addition some evidence which suggests that further regulating mechanisms exist, which provide for the elimination of

fluid through the capillary walls. These act in such a way that interference with the function of the heart or kidney or a localized disturbance in certain tissues, which would tend to change the amount and composition of the circulating body fluids, leads to an increased transudation of fluid from the blood capillaries into the tissues and into the serous cavities. In certain respects such an increased transudation may be considered as a safety process tending to maintain the condition of the blood constant. But if this last mechanism is more than a transitory expedient, which is at once compensated for by increased absorption, it becomes pathological in itself and represents edema.

The water contained in the circulating body fluids as well as in the interstitial tissue and in the tissues proper enters into relations with salts and colloids, particularly proteins, and both of these substances thus become factors which help to determine the quantity of water which is held in various parts of the body, and which influence the passage of fluid through the membranes separating the blood and lymph channels from interstitial tissue, serous cavities and organ tissues proper. In addition, evidence has been found in recent years which shows that various organic substances, among which are certain hormones, may influence likewise the direction of the movement of the body fluids and may thus become a factor in the abnormal accumulation in, and in the discharge of fluid from the body.

We see then that the factors underlying edema are not identical with those determining the formation of lymph, although both have some factors in common, namely, transudation and tissue activity; but elimination through the lymph channels may play a certain part in compensating for an increased transudation, and obstruction of the lymph channels in certain cases may lead to a back current of fluid into the interstital tissue. However, the production of edema depends on conditions which are not necessarily directly concerned in lymph formation and an analysis of edema is therefore not identical with an analysis of lymph formation.

Interference with any of the factors which participate in the regulation of the mechanisms which tend to maintain what might be called homoiohydria and homoiotonicity may lead to edema. Deficiencies in the movement and distribution of blood, in the elimination of fluid through the kidney and in the transudation and absorption process

through capillaries and lymph vessels may lead to edema, but these various factors are of unequal importance in so far as faulty movement of blood and faulty elimination of fluid affect the transudation process, and act therefore essentially through an interference in the exchange of fluid between the capillaries and tissues.

As in other functions of the living organism, we have in some of these mechanisms, which regulate the distribution of fluid in the body, to deal with chain reactions in which an initial change or stimulus leads to a series of subsequent changes. Some of the elements constituting the different chains may be identical and the same elements of a chain may thus recur in several series.

A perfect analysis of edema would presuppose a complete knowledge of the various chains and especially of those elements of chains which are found in several or all of the series. These elements we would consider as the real causes of edema. However, at present our knowledge of the various chains is still incomplete, although we know some of the important elements of the chains which recur in several series, and in particular are we unable at present to state in most cases the sequence in which the different elements are joined to each other.

This consideration is of some importance in the classification of the various kinds of edema. We might use for the purpose of classification the initial factors in the various chains, or, on the other hand. we might try to sift out the important elements in the reaction chains which follow the initial interference.

As we stated, these elements are insufficiently known; the relative importance and sequence of various elements are uncertain; furthermore, similar elements recur in different series. A classification based on these elements would therefore be uncertain. We shall discuss the various chains separately and use for classification the initial elements of the chains. In each case the essential object of investigation concerns the character of the succeeding elements and the order in which they follow each other.[1]

[1] We shall consider in more detail the publications of approximately the last fifteen years and make only brief references to the older literature. More complete references to the latter are found in Meltzer, Lectures on Edema, American Medicine, 1904, Vol. 8, p. 19 and subsequent numbers. R. Magnus, Bildung d. Lymphe., Handbuch d. Biochemie Vol. 2, II, p. 99. H. Gerhartz, ibid., p. 137. R. Klemensiewicz d. Pathologie d. Lymphstroemung. Handbuch d. allgem. Pathologie (Marchand u. Krehl), Vol. 2., I Ab., p. 341. See also a presentation of edema by H. G. Wells, Chemical Pathology, III Edition, p. 339, and M. H. Fischer, Edema and Nephritis, New York, 1915.

II. CHANGES IN THE PERMEABILITY OF BLOOD-VESSELS IN LOCALIZED EDEMA

A. Varieties of local edema

Some of the most important recent contributions to the study of edema concern an analysis of the factors that influence the permeability of blood-vessels, and the significance of these factors in the origin of edema. However, the conception of a change in vascular permeability as a cause of edema is rather old and the first observations reach back a considerable number of years. In order to appreciate the significance of these factors, it is necessary to give a brief résumé of the more important investigations gradually leading to the recognition of a variable permeability of the capillaries as a factor in the origin of edema.

Grainger Stewart and Bartels had expressed the opinion that renal edema was caused by a retention of water, the result of renal deficiency. The experiments of Cohnheim and Lichtheim did not altogether substantiate this view. The later investigators showed that small amounts of sodium chloride solutions could be injected intravenously into rabbits without edema developing subsequently. However, when very large amounts were infused, ascites and edema of the gastrointestinal canal, around certain glands, and in restricted parts of the interstitial tissue elsewhere, resulted; but the thoracic cavity and particularly the subcutaneous tissue remained essentially free from edema. When, however, local irritants (iodine, heat) were applied to the skin, the experimental hydremic plethora was followed by an edema in the affected area. Likewise, ligating the femoral vein, which in itself did not lead to edema, caused edema in hydremic animals. Similarly a temporary complete interruption of the circulation in a certain area may lead to edema of this area after the reestablishment of the circulation. Several conclusions may be drawn from these experiments: (1) A hydremic condition of the blood does not necessarily lead to edema. (2) It may lead to edema in parts of the body, when combined with an increased permeability of the vessels, where hydremia alone did not have this effect. (3) Hydremia in conjunction with passive congestion also may lead to edema. (4) Increased permeability of the vessels alone may give origin to edema.

These conclusions were confirmed and extended by Magnus who showed that intravenous perfusion of dead rabbits with a solution of sodium chloride led to general edema (including anasarca). In the living animal poisoning with arsenic and other substances, which were supposed to affect the blood-vessels, as well as a preceding occlusion of the ureters had similar consequences in the perfused rabbits.

However the significance of an increase in the permeability of vessels as the cause of edema can be shown more directly through the study of localized edema. These edemas furthermore lend themselves more readily to an analysis of the action of substances influencing the permeability of the capillary blood-vessels and thus modifying the course and intensity of edema.

To this category of localized edema belongs in the first place the edema accompanying inflammation. Related to the ordinary inflammatory edema are localized edemas which occur in conditions, which are either anaphylatic in character or at least closely resemble anaphylatic phenomena. The reaction against tuberculin in individuals infected with tubercle bacilli, or injected with certain of their products, the positive Schick and Luetin tests, are of such a character. Whether these reactions are truly anaphylatic or merely resemble anaphylatic reactions is a matter of dispute at the present time.

Edematous conditions resembling the exudative diathesis of Czerny which occurs in childhood may in some cases be due to anaphylaxis (Schultz and Larson). In sensitized individuals in whom a second injection of the antigen has been given, a non-specific irritation of the skin may cause a very pronounced edema, which Auer interprets as due to the accumulation of antigen in the lymph at the place of irritation. In urticaria or in related conditions, such as are caused through the ingestion of certain substances in predisposed individuals or through intradermal injection of certain substances like histamin (Eppinger), morphine, atropin, formaldehyde, concentrated calcium chloride (Philippson, Th. Sollmann and Pilcher), we have to deal with a localized edema, probably due to alteration of capillaries (Gilchrist, Jadassohn and Rothe). There is not only transudate present in these cases, but even some emigration of leucocytes and edematous swelling of cells and connective tissue fibers. Certain substances like arsenic, chloral, salicylates and others, which produce clinically

urticaria, do not have this effect after intradermal injections. Local acidosis can be excluded as the cause of these edemas (Sollmann and Pilcher).

Related to this class of edemas is the toxic edema which is produced through bacterial toxins or through the action of light in individuals, in which a photosensitizing fluorescent substance is circulating in a quantity sufficient to cause an injurious effect of light rays. Thus Hausmann could produce extensive edema of the skin in mice injected with haematoporphyrin and subsequently exposed to light. If the Laewen-Trendelenburg blood-vessel preparation is perfused with fluid which contains fluorescent substances, edema is produced in the perfused legs (Adler). In these cases the vessels are probably injured through the circulating fluid. Certain exudative skin affections are perhaps due to the combined action of a sensitizing substance and light.

A similar injury to the endothelial cells of the capillaries may, according to Findlay, explain the edema which is found around the capillaries in the scurvy of guinea pigs. Deficient nourishment produces an injury to the wall of the capillaries, which at first allows only the escape of plasma from the blood-vessels; and only if the injury becomes more marked an escape of erythrocytes follows. We may assume that the permeability of the capillaries is thereby sufficiently increased to cause edema.

Somewhat related to this toxic effect on the endothelia of blood-vessels in the Laewen-Trendelenburg preparation is the edema produced in this preparation, if, according to Zwaardemaker and Ginzburg, Locke solution which has been deprived of its potassium content, is used as a perfusing fluid. These authors attribute this result to the lack of the beta rays given off by the radioactive potassium and they are able to substitute for potassium certain other radioactive substances in definite proportions and thus prevent edema. These experiments likewise point towards the reaction of the endothelium as an important factor in edema. Of interest is also the observation of these authors, that uranium or other heavy radioactive substances, while beneficial if acting as substitutes for potassium or rubidium, may antagonize the effect of potassium if used in combination with this substance. This effect may possibly have to be considered in explaining the very marked edema producing power of uranium salts.

These observations are however interpreted differently by R. T. Hamburger, who finds that the relation of Ca, Na, and K ions in the perfusing fluid is the determining factor. A certain concentration of Ca ions tends to make the capillaries impermeable and at the same time causes a constriction of the vessels, while potassium ions, if not counteracted by calcium, tend to have the opposite effect. Hamburger finds that a mixture of Na and Ca ions is able to prevent edema, provided Ca ions are present in sufficient quantity. Potassium ions are not necessary for this purpose.

We shall again refer to the significance of the capillary wall in the production of edema and particularly to the analysis of variable factors concerned in this process in the next chapter, where we shall discuss still further the factors which affect the permeability of blood-vessels.

Under certain conditions the application of alkali increases the permeability of the skin. Thus Jacoby has shown that alkali and veronal, as well as saponin, make it possible for very small amounts of adrenalin, which alone would be ineffective, to penetrate the frog-skin and to affect the vessels. This author suggests that carbon dioxide may increase the permeability of the capillaries indirectly by making available OH ions, which would combine with lipoids or proteins of the cells and thus influence the permeability of the latter.

Various authors attribute also edema of renal origin to a generalized change in the blood-vessels. They assume that uranium nitrate produces changes in the permeability of the blood-vessels. Functional alterations in the vessels following the administration of this substance we shall discuss later in connection wtih renal edema. Fleckseder found in addition structural changes in the renal vessels and peritoneal ecchymoses after administration of uranium, but these findings hardly permit the conclusion that uranium salts cause structual changes in the blood-vessels generally.

In this connection we may also discuss the so-called angioneurotic edema. It is a localized edema which is particularly prone to appear in the skin, but may also appear in mucous membranes or in the brain. H. Quincke, who designated it "angio-neurotic edema," assumed formerly that it was caused by a localized and transitory change in vasomotor function. Two kinds of data seem to support such a conclu-

sion: (1) It has been observed that it may occur under the influence of emotions and in hemicrania. Its unilateral localization might suggest a more peripheral point of attack of the nervous mechanism. (2) Certain experimental facts indicate that hyperemia, caused through paralysis of a sufficient number of vasomotor nerves, may call forth an increased transudation of fluid from the blood-vessels into the tissues and temporarily an increased lymph flow in this area. In these cases however the transudate does not usually accumulate in the tissues and edema does not ensue. Active hyperemia also may lead to increased transudation and even to edema. The latter has been produced through electric stimulation of the peripheral end of the lingual nerve in dogs. If the hyperemia is sufficiently strong and long continued, edema of half of the tongue may follow. While we must thus concede the possibility that vasomotor nerve changes may lead to localized edema, it is by no means certain that this is the mechanism which actually is implicated in the so-called angio-neurotic edema. Indeed H. Quincke himself has recently abandoned this interpretation and holds changes in the tissues, which lead to an increased attraction of water, primarily responsible. But this too is merely a hypothetical assumption.

In analogy to other strictly localized edemas it appears most probable that changes in the permeability of blood-vessels in circumscribed areas, due to the action of toxins, are the direct cause of this kind of edema. Some cases of the so called angioneurotic edema seem to be due to a hypersensitiveness to certain proteins, especially those contained in food. They would thus represent types of localized, exaggerated urticaria (observations of Walker, Phillips and others).

In certain cases the tendency to this edema seems to be inherited. Cases of inheritance have been observed by various authors and recently a similar observation has been reported by the Crowders.

B. Functional and toxic changes in the permeability of blood-vessels. Inflammatory edema

Recent observations tend to prove that dilatation of the capillaries increases the permeability of the vessel wall and is followed by a movement of blood plasma from the interior of the vessel to the

surrounding tissue. Sherrington and Copeman found that various operative procedures, especially those tending to produce shock, caused an increased specific gravity of the blood, and they interpreted this as due to a movement of the blood plasma from the vessels into the tissues. According to Heubner a series of substances act as capillary poisons, diminishing the tone of the endothelial cells, leading to a dilatation of the capillaries, to stagnation of the blood and to a lowering of blood pressure, thus bringing about a condition comparable to internal bleeding. But these substances may also cause true hemorrhages by diapedesis, as the result of a loosening of the cement substance between the endothelial cells. Emetin, sepsin, salts of heavy metals (gold, sodium salts) may act in this way. More recently Dale, Laidlaw, Richards and Rich have shown that histamin causes on the one hand a dilatation of the capillaries and a movement of the plasma from the blood vessels to the tissues, and on the other hand a contraction of the smooth muscle layer in arterioles and bronchi. Application of this substance thus imitates the conditions found in shock. The studies, particularly of Krogh, Hooker and others, have made certain the general conclusion that capillaries can contract and dilate independently of changes in the arterial wall. Chemical as well as mechanical stimuli may have such an effect, producing especially vasodilatation. Few substances lead to constriction. Adrenalin in larger doses seems to act thus, while in smaller doses it may lead to a dilatation.

A direct demonstration of the escape of plasma through pores in the capillaries, after chemical stimulation through urethan, has recently been given by Krogh and Harrop. Soluble starch and colloidal dyes leave the blood vessels under those conditions, while particles of India ink are held back. An increase in intracapillary blood pressure is not responsible for this increased permeability.

According to Hooker chemical stimulation leads to a dilatation of capillaries and increased transudation, while nerve stimulation counteracts these influences. Krogh has furthermore shown that every normal muscular activity leads to a dilatation of the capillaries. An increase in permeability occurs in response to tissue needs, if carbon dioxide and other metabolic products accumulate (Krogh). Hess and Fleisch have shown generally that a physiological increase

in hydrogen ion concentration in actively metabolizing tissue may lead to a dilatation of the blood-vessels.

This dilating effect of stimuli explains the condition in inflammation, particularly the production of inflammatory edema. If the dilatation caused by abnormal stimuli is sufficiently marked, plasma leaves the vessels, the viscosity of the blood increases (Trevan) and stasis may result.

Quite recently Krogh and Rehberg have made it very probable that pituitrin maintains the tonus of the capillaries. Ringer's solution alone, serving as a perfusion fluid for the blood-vessels of the frog, causes a dilatation of the capillaries and *pari passu* an escape of the fluid from the vessels into the interstitial tissues. Addition of pituitrin in very low concentration prevents this process by maintaining the tonus of the capillaries. There is reason for assuming that the substance present in the normal serum, which has a similar effect on the vessels, is identical with pituitrin.

In this connection we must again refer to the influence of ions on the permeability of the blood-vessels. Gunzburg found that if the frog preparations are perfused with Ringer's solution, edema does not follow, but if potassium is omitted from the solution the legs become edematous. Subsequently R. J. Hamburger has shown that the permeability of the capillaries depends on the quantitative relation between Na, K and Ca ions in the perfusing solution; in the same way as in some other cases Ca counteracts also in this case the Na and K ions. A fluid consisting of Na and Ca ions used in correct proportions prevents edema, even if potassium is absent. Addition of too much potassium on the other hand caused edema. Calcium causes a tightening of the vessel wall and if added in still larger quantity to the sodium chloride solution, it may produce an extreme contraction of the vessels. It may be assumed that the tightening of the vessel wall, resulting in lessened permeability, and the process of constriction of the vessels are related and associated processes. As we have shown previously the contrary condition also holds good, a dilatation of the capillaries may be accompanied by a greater permeability of the vessel wall. In a similar way an increase of the oxygen tension of the perfusion fluid tightens the vessels, prevents edema and may cause contraction of the vessel wall.

There is also some direct evidence pointing to changes in the permeability of blood-vessels in the origin of experimental or clinical edema. Quite recently Morawitz and Deneke have devised a method which enables them to recognize functional changes in the permeability of the blood-vessels. They determine a change in the concentration of the blood following a compression of the vessels of the upper extremity. An abnormal reaction indicating an increase in permeability was observed in acute and chronic glomerulonephritis, but also in certain other diseases even if they are not accompanied by edema, as for instance, typhoid, scarlet fever, purpura, endocarditis and carbonmonoxide poisoning. In these latter diseases there is indeed some reason for assuming the presence of vascular lesions; on the other hand in a case of cardiac edema and in edema due to undernourishment, normal vascular reactions were found. We would then have to assume that in the latter kinds of edema vascular injuries are not a prominent factor in the causation of edema, in contradistinction to kidney lesions where they are of etiological significance. While in experimental conditions leading to edema, particularly in uranium nitrate poisoning, changes in the permeability of blood-vessels have been found also by other means, they are the opposite of what might have been expected. Thus Boycott and Chisholm and others found a slowing of the rate of elimination of certain substances from the blood-vessels in the later stages of uranium poisoning, a condition in which edema is a prominent feature. We shall have occasion to refer to these experiments again in a subsequent chapter.

While, thus, recent investigations clearly demonstrate the importance of changes in the permeability of membranes in the origin of inflammatory and toxic edema, there has also been forthcoming some new evidence which tends to show that there must be added to the increase in permeability filtration pressure, if edema is to result. Thus Hirschfelder has shown that the inflammation, which in the rabbit follows instillation of mustard oil in the conjunctival sac, requires a certain intensity of blood pressure. In animals, in which through measures of a mechanical or toxic character, the blood pressure has been lowered to a certain level, edema does not develop. Even injection of peptone, which as a lymphagogue of the first order is supposed to increase the permeability of membranes and thus

increase edema, may prevent edema, if it causes a fall in blood pressure below a certain level.

We may then conclude that functional as well as toxic influences cause frequent variations in the permeability of the blood-vessels. It may be assumed that there is a graded increase in permeability from that produced by purely functional conditions to that caused by toxic and inflammatory stimuli in general, which latter permit even cellular motile elements to pass through the wall of the vessels. The greater the permeability, the greater the amount of molecules of large size and particularly of colloids, which can pass through the vessel wall.

Even with normal capillaries, a certain amount of colloid passes out of the blood-vessels together with water and salts. A reverse current also occurs. While in certain cases protein-free fluid can perhaps enter the blood-vessels, usually some protein is mixed with this fluid. This for instance can be shown to be the case if a relatively large quantity of water is administered to a rabbit. At different periods water moves in this case in or out of the blood-vessels, together with some protein (Oehme). The character of the diet given previously determines to some extent the direction in which the fluid moves. Nonnenbruch likewise observed that protein may move with the water into the blood-vessels. This fact makes it clear that refraction determinations cannot serve as a satisfactory indicator of changes in the blood volume.

In some respects the vessel wall may be compared to a membrane, the properties of which are variable, but which in general retains more readily large molecules than smaller ones and through which, for instance, solutions of glucose are held back to a greater extent than sodium chloride solutions. It may behave on the one hand like the filters devised by Bechhold for ultrafiltration, or it may resemble a filter with relatively coarse pores; there are all kinds of graduations between these two extremes. In general we may state that factors which tend to cause a dilatation of the vessels and to decrease the tonus of the capillaries, tend to increase the permeability of the vessel wall and thus to favor the production of edema, and that contraction of the vessels has the opposite effect. These variations in permeability of the vessels are an important factor in the origin of edema.

C. Shock and edema

While shock, experimental or clinical, is not known as a cause of edema, still the intensive study of shock made during the recent war is not without interest for the analysis of certain factors that underlie edema. Cannon designated as exemia, a condition preceding and responsible for shock; it is an overfilling of capillaries with blood in certain areas of the body and a transudation of plasma from the vessels into the tissues. These two factors cause a diminution in the efficient blood volume. Dale, Laidlaw and Richards have shown this condition to be very pronounced in shock produced by injection of histamin. Erlanger, Gasser and Gesell analysed the circulatory factors in a variety of conditions associated with shock and found, common to all of them, an engorgement of the splanchnic capillaries and vessels with blood and a considerable transudation of plasma, as the result of a localized slowing of the circulation combined with a dilatation of the capillaries; in addition there may be an increase in capillary pressure in certain cases. Of special interest is the observation of these authors that if shock follows injection of adrenalin, each successive injection of adrenalin produces a concentration of blood greater than the preceding one. Each injection must therefore have left a residuum of damage which became so intense after the third injection that the plasma did not return to the vessels as before; in the non-injured body, on the other hand, according to the interpretation of Starling, the plasma is supposed to return to the vessels in places, where the blood pressure is lower. Thus we have brought about a condition which, if continued over a sufficient period of time, would lead to edema.

To counteract this diminution in the effective blood volume in shock, Bayliss used an isotonic solution of the colloid gum acacia, while Erlanger and Gasser employed hypertonic solutions of this substance in combination with a hypertonic solution of glucose. They find that the acacia injected intravenously attracts water very slowly into the circulation as compared with the crystalloid glucose. It does not hold the water in as large a quantity as would be expected on the basis of its osmotic pressure and the maximum blood volume reached is not maintained, although the blood volume is held at a higher level longer than after injection of hypertonic solution of glucose.

F. E. Meyer and Seyderhelm find a Bayliss solution effective in counteracting the influence of a loss of blood on the size of the heart, in contradistinction to Ringer's solution which is not effective in this respect. On the other hand, according to Nonnenbruch, after intravenous injection of a Bayliss solution in rabbits, the blood volume returns to the normal condition as early as two to three hours following the injection; in this respect it acts not differently from Ringer's solution. The injection of hypertonic acacia solution, on the other hand, this author finds more effective.

The hypertonic acacia-sugar solution thus prevents, during the period of acute shock, an excess of plasma from leaving the circulation, provided the damage to the vessel wall has not caused a very considerable increase in the permeability of the blood-vessels.

We see then in shock the same increase in transudation of plasma which is characteristic of edema; but in shock we have to deal with an acute condition, in which a considerable part of the fluid returns to the vessels, and in which the process of transudation, lasting only during a relatively short period of time, is not sufficiently extensive to become manifest as edema. At the same time we have found indications that the beginning of edema may be produced experimentally in these conditions, provided a gradation in intensity of the shock is accomplished.

D. The rôle of sensory nerves in inflammatory edema

G. Spiess drew attention to the fact that local anesthesia prevents or diminishes the edema which is due to the action of toxic substances. He attributed this effect to the elimination of pain, which latter was supposed to cause a reflex dilatation of the blood-vessels. Thus inflammatory edema may be lacking in anesthetic areas, even in those found in cases of hysteria.

In accordance with this conclusion Januschke found that the edema following the application of mustard oil can be prevented not only by the use of calcium salts, but also by adrenalin and various anesthetizing substances, like ether, morphine, chloralhydrate and also by antipyrin, quinine and sodium salicylate. According to Starkenstein and Wiechowski injection of atophan has a similar effect; this latter observation was however not confirmed by Heubner.

The effect of anesthetics upon inflammatory edema suggested the participation of reflex mechanisms in this process. The mechanism of dilatation of vessels in inflammation which is followed by transudation has been analysed by A. N. Bruce, who concludes that it is due to an axon reflex. The application of alypin prevents this inflammatory reflex. Brady, on the other hand, interprets this reflex as due to the stimulation of sensory nerves which inhibits the constricting action of sympathetic ganglia, and thus leads to an inflammatory dilatation of the vessels. Anesthesia, in eliminating this inhibiting effect of sensory nerves, maintains the constricting action of the sympathetic ganglia.

However more recent experiments do not entirely confirm these conclusions. According to Breslauer a local reflex, which may be inhibited through local anesthesia of the affected skin or mucous membrane, is responsible only for the primary active inflammatory hyperemia; the later phases of inflammation on the other hand are not influenced by local anesthesia. Elimination of pain sensation is not concerned in this process. Different again are the conclusions of Groll, who finds that anesthesia, or even degeneration of the nerves leading to a certain area, is not capable of preventing the primary inflammatory hyperemia which he considers as paralytic. However, cocain as well as various other anesthetic substances, can diminish the chemosis following the application of mustard oil to the conjunctiva. The effect of these substances cannot be due entirely to vasoconstriction, because atropin and veronal which dilate the vessels have a similar influence. He concludes that substances producing inflammation act directly on the neuromuscular apparatus of the blood-vessels.

It is probable that the effect of anesthetics and some other substances in diminishing certain phases of the inflammatory reactions and particulary inflammatory edema, is due mainly to their direct action on the neuromuscular apparatus of the blood-vessels, but in addition they may perhaps also cause a vasoconstriction by reflex mechanisms. However that may be, for us it is important to know that various substances are able to diminish the transudation from the blood-vessels through their effect on the permeability of the blood-vessels. In certain cases this diminution in the permeability of the blood vessels

is apparently associated with a constricting effect on the blood-vessel wall (adrenalin); in other cases these substances prevent directly or reflexly a dilatation of the capillaries and an increased permeability.

Above we have referred to the experiments of Hirschfelder which have shown that, in addition to the factors named, a certain intensity of blood pressure is a necessary condition for the development of this inflammatory edema. A lowering of the blood pressure below a certain point may prevent it because it is the filtration pressure which drives the fluid across the vessel wall into the surrounding connective tissue. However, under normal conditions the filtration pressure required for transudation is always present; the variable factor is therefore the change in the permeability of blood-vessels; this is altered in inflammation and to a less degree it varies under normal conditions, in accordance with functional variations in the vessels and in the surrounding tissue. Under certain conditions however the filtration pressure may increase to such an extent that this rise may become a factor in the increased transudation and even lead to edema. This holds particularly good in regions where the blood-vessels possess normally relatively considerable permeability.

E. Calcium and edema

There exists an antagonistic action between the bivalent calcium and the monovalent sodium ion which is apparent in many physiological functions; while sodium tends to stimulate, calcium has an inhibiting effect.

According to Jacques Loeb and Osterhout this inhibiting action of calcium depends on a diminution in the permeability of the cell membrane which this ion produces. Sodium on the other hand increases this permeability. Osterhout assumes that calcium and sodium combine in definite proportions with a constituent of the cell, and that, according to the relative proportion in which these two combinations of the cell constituent, with either sodium or calcium, are present, the permeability of the cell varies.

R. Hoeber and R. S. Lillie especially referred the antagonistic action of sodium and potassium ions, on the one hand, and of bivalent ions on the other hand, to their effect on cell colloids. While the monovalent kations tend to exert a softening or dissolving effect, the bivalent

ions and particularly calcium have an opposite, hardening, coagulating effect on the cell colloids. Similarly Herbst has shown that without the presence of calcium salts the blastomeres of the echimoderm egg separate from each other, while they join again after addition of these salts.

In a somewhat different way Clowes explains the effect of calcium on the permeability of membranes. He found that addition of calcium chloride to an emulsion of oil in water tends to transform this emulsion into the reversed emulsion of water in oil. This change would necessarily lead to a decreased permeability of a membrane consisting of such an emulsion to substances soluble in water, but insoluble in oil.

These facts suggested the conclusion that calcium salts might exert an influence on edema. In 1896 A. E. Wright first proposed the use of calcium in the treatment of various hemorrhages and of urticaria, which latter represents an edematous condition of the skin. This author based his recommendation on the effect of calcium in the clotting of the blood. However, the first experiments dealing with the influence of calcium salts on the formation of transudates were to our knowledge carried out by Fleisher, Hoyt and Leo Loeb and by Fleisher and Loeb. We compared the effects of the intravenous injection of isotonic sodium chloride solutions on the one hand, with those of a mixture of four parts of this solution and one part of a calcium chloride solution on the other hand. In a very extensive series of experiments we found that calcium chloride diminishes the quantity of urine and of intestinal fluid, which are both augmented through the intravenous injection of sodium cloride solution. We could furthermore show that the effect of calcium on the kidney was not due, as had been maintained by Porges and Pribram, to a lowering of the blood pressure caused by the injection of this substance, but to a direct action on the kidney cells. This was proven in experiments in which we combined calcium chloride with adrenalin, which maintained the blood pressure at a considerable height and still we obtained the typical calcium effect. Similarly calcium affected the secretion into the intestines directly and not indirectly through the circulation, as experiments showed in which we compared the calcium action with the effect of an experimentally produced myocarditic lesion in rabbits; this latter

likewise causes a lowering of the blood pressure and a diminution in the amount of urine. The fall in blood pressure caused by the myocarditic lesion did not affect the amount of intestinal fluid. While thus calcium exerted a markedly inhibiting effect on the secretion of urine and intestinal fluid, it increased, on the contrary, very noticeably the transudation of fluid into the peritoneal cavity, and it increased also the incidence of pulmonary edema. This increase was found not only in normal rabbits, where calcium might cause a retention of fluid by diminishing the amount of urine and of intestinal secretion, and thus increase the amount of peritoneal transudate only indirectly, but it was manifest even in nephrectomized animals, where such an interpretation could not hold good.

We may thus conclude that the elimination of fluid into the peritoneal cavity follows laws altogether different from those governing the secretion through kidney and intestines. We could furthermore show through comparison of the effects of calcium chloride with those of myocarditic lesions that alterations in the blood pressure are not an important factor in the formation of the peritoneal transudate caused by intravenous injections of these solutions. In a similar way, while the absorption from the intestines is diminished by calcium, the absorption from the peritoneal cavity is not inhibited by this substance.

Furthermore according to our observations calcium chloride, in the proportions in which we added it to the blood, does not influence in a noticeable way the elimination of fluid from the blood-vessels, neither retarding nor accelerating it. On the other hand, after a preliminary rise it causes a marked fall in blood pressure. We may then conclude that calcium affects the amount of ascitic fluid in one of two ways: it either acts directly in a specific manner on the endothelial lining of the serous cavities, or it diminishes the storing of water in those tissues which normally act as reservoirs for water, especially the muscles and the skin.

In apparent contradiction to our results, which are based on a large series of concordant experiments, are the subsequent investigations of Chiari and Januschke. These investigators found that subcutaneous injections of calcium salts in rabbits, given previous to the application of mustard oil, prevents, or at least noticeably diminishes, the inflammatory edema following an application of mustard oil to the

conjunctiva. They also found that these salts prevent edema of the lung and the formation of pleural exudate, which result from the injection of diphtheria toxin and of sodium iodide.

As far as the influence of calcium salts on the formation of pleural exudates is concerned, the results of Chiari and Januschke could not be confirmed by subsequent investigators (R. Levy, H. Leo, Muller and Saxl). L. Pollak likewise found that calcium salts do not inhibit the formation of peritoneal transudate in rabbits poisoned by uranium nitrate. Neither does calcium seem to exert a decidedly beneficial therapeutic effect on the inflammatory edema caused by mustard oil, but on the other hand the prevention or mitigation of inflammatory edema by injections of calcium chloride previous to its onset has been confirmed by various authors (R. Levy, Heubner, Luithlen). Also the inflammatory exudate caused in the pleural cavity by local application of turpentine can be diminished temporarily through calcium; but on the second day this mitigating effect of calcium chloride has disappeared (R. Levy).

The action of calcium salts in this respect, however, cannot be very striking. Cushny, in repeating Chiari's and Januschke's experiments with mustard gas, obtained negative results, and, in agreement with Fleisher and Loeb, Bayliss found that an excess of calcium chloride added to Ringer's solution does not retard the elimination of the fluid from the blood-vessels. According to Sollmann a concentrated solution of calcium chloride applied intradermally not only does not prevent, but it even causes edema (urticaria). According to Laqueur and Magnus under certain conditions calcium chloride administered subcutaneously may, to a slight extent, diminish the pulmonary edema caused by inhalation of irritating gases, while after intravenous injection it may, on the contrary, increase edema, as our experiments have shown.

It is certain that calcium decreases the secretion of urine and increases the formation of transudates in normal animals, if injected intravenously. On the other hand, Maase and Zondek as well as E. Schultz observed that the acute war edema was influenced favorably by administration of this salt. W. Hülse finds furthermore that calcium salts given orally in large doses effect a rapid discharge of renal edemas in many cases, even when other means have been found

ineffective. It also influences the nephritic process beneficially. This author interprets this effect as due to the diminution in the water binding power of colloids, which is caused by bivalent kations.

It is not probable that these apparently contradictory statements are due to errors of observation. Calcium seems to exert various functions under different conditions. Its preventive effect on inflammatory edema may possibly be due to a constricting action on blood-vessels and to a decrease in permeability of the endothelium. Haffner observed that calcium chloride may cause an intense constriction of vessels—an observation which agrees with those reported in a preceding chapter—and according to Rosenow and Starkenstein it delays the absorption and elimination of fluorescin through the blood-vessels. This agrees also with the fact that Exner and Meltzer and Auer have shown that adrenalin causes a delay in absorption and that Rosenow observed that adrenalin acts similarly to calcium salts in inhibiting the formation of inflammatory exudate. Inasmuch as we know that adrenalin exerts its effect through causing constriction of the vessels, we may consider the possibility that calcium chloride acts similarly. In agreement with this fact is the observation that the action of calcium chloride in inflammatory edema is of a transitory character.

We have referred above to the observations of Günsburg and Hamburger on the effect of salt solutions on edema in perfused frogs. Hamburger has shown that Ca added in a certain proportion to a 0.6 per cent NaCl solution may prevent edema in the frog-leg, which a NaCl solution alone would produce. In a favorable proportion Ca may make the vessel wall less permeable and this effect is related to a contraction of the vessel which occurs under the influence of a slightly stronger solution. A sufficient supply of oxygen likewise decreases the permeability of the vessels and causes their contraction. These observations support then the view of the connection between a decrease in permeability and an increased contraction following an increase in Ca ions.

Now, while under certain conditions, if used in certain proportions, calcium may decrease the permeability and thus prevent edema, in other proportions it may perhaps have the opposite effect. Thus according to H. I. Hamburger calcium diminishes the permeability of the glomerulus epithelium for sugar, if used in medium concentra-

tion, but it increases it if used in larger or smaller concentration. It acts in a similar manner in hemolysis and certain other conditions. This might explain the apparent differences in our results and in those of Chiari and Januschke. It might also be that calcium affects the peritoneal endothelium and the vascular endothelium differently. As to the occasional beneficial effect of calcium in cases of renal edema, some additional explanations have been suggested. Thus it has been assumed that calcium may counteract the effect of sodium and in this way neutralize one of the important factors responsible for renal edema. Hülse suggests in addition that calcium may cause a disappearance of the spastic constriction of preglomerular vessels and thus make possible a better perfusion of the kidney with blood; or it may diminish inflammatory conditions in the kidney in cases of nephrosis and thus aid in the elimination of sodium chloride and water (Starkenstein). It is of course possible that in addition calcium chloride exerts an influence antagonistic to sodium chloride within the tissue.

In recent studies Blum, Aubel and Hausknecht interpreted the beneficial action of calcium chloride in renal edema as due to its effect on the elimination of sodium. Bunge had previously found that ingestion of potassium salts leads to an increase in the excretion of sodium through the urine. These authors confirm Bunge's conclusion and extend it to calcium, which likewise increases the elimination of sodium through the kidney. Now, according to Blum, the current of water always follows the movement of sodium. Therefore elimination of the sodium leads to a discharge of edematous fluid. In this manner calcium chloride diminishes the sodium content of the blood and prevents the latter ion from migrating from the blood into an area of inflammation and at the same time drawing with it a current of water. In a similar manner they explain the experiment of Chiari and Januschke on the effect of calcium in preventing the inflammatory edema caused by instillation of mustard oil.

In case the kidney is not very permeable to sodium, calcium and potassium may have the opposite effect, causing an increased elimination of sodium into the ascitic fluid. Calcium and potassium salts would thus not only not decrease the amount of edematous fluid, but on the contrary increase it. However, inasmuch as it has not yet been shown that the effects of calcium and potassium run a parallel course, this explanation is still hypothetical.

As to the mechanism by which calcium chloride leads to the elimination of sodium, another explanation has recently been suggested by Frey. He assumes that after administration of calcium chloride the calcium is principally eliminated through the intestines, while the anion is excreted through the kidney and draws with it the sodium ion, thus leading to the discharge of the latter.

But the fact that intravenous administration of a calcium salt leads to the discharge of the edematous fluid even in cases of cardiac decompensation and in cardiorenal disease, suggests that calcium may under these conditions act in a way similar to digitalis, strengthening the heart action, diminishing the frequency of the pulse and lowering the blood pressure (Singer). It would therefore cause the discharge of the edematous fluid in a manner similar to digitalis, namely, through removal of those circulatory defects which were responsible for the origin of edema under these conditions.

We have evidently to deal with an interaction of different mechanisms. This seems the more probable, as we know that the effect of calcium on inflammatory edema is not strictly specific. We have mentioned above that anesthetics may have a beneficial effect and a similar effect is exerted by adrenalin. In addition Januschke found that magnesium sulphate likewise may prevent inflammatory edema, even in doses which are not large enough to cause anesthesia.

The effects of calcium are then as follows: Calcium salts administered intravenously may increase the amount of transudates in animals. The mechanism through which calcium influences the formation of urine and intestinal fluid, differs therefore from that through which it influences transudation. It may diminsh the permeability of the blood-vessels and cause their contraction under certain conditions and may thus prevent the inflammatory edema following the local application of certain irritating substances. This effect is, however, not strictly specific. Calcium has no curative effect, once the inflammatory edema has been produced. It does not diminish the amount of inflammatory transudates in the serous cavities, nor does it noticeably influence the transudation of fluid through the blood-vessels. However, in a manner similar to potassium salts, calcium salts may, in certain cases of renal or cardiac edema, lead to a discharge of edematous fluid. The mechanism through which this

latter calcium effect is accomplished is as yet doubtful, but it may be that the action is an indirect one and that it is due to the acceleration in the elimination of sodium following the administration of calcium; or in case of cardiac or cardiorenal disease, it may be due to an improvement of the circulation.

Calcium is furthermore necessary to balance the effect of sodium on the permeability of the blood-vessels. Too large a proportion of sodium or potassium chloride increases the permeability of the blood-vessels while calcium added in a certain proportion counteracts this effect.

F. Conclusion

Recent studies of the circulation, especially of the capillaries, bring evidence that the permeability of these vessels is a variable factor which in some way runs parallel to their state of dilatation in response to functional as well as pathological conditions, and that pathological stimuli may cause a still further circulatory change and may in particular call forth an increase in the capillary permeability. This permeability is a graded one permitting elements of different sizes to pass through the vessel walls. Thus colloid particles of various sizes may leave the vessel wall and fill the interstitial spaces around the vessels. All the evidence points to the conclusion that these changes in vascular permeability are important factors in various kinds of edema, primarily in those of a localized character, but they play probably a similar rôle in some generalized edemas. Related conditions exist in shock, where a state of frustrated or abortive edema exists; however, the character of shock, being a transitory condition, precludes the development of a renal edema. In certain of these acute circumscribed edemas, hereditary factors may play a part.

III. GENERALIZED EDEMA DUE TO DEFECTIVE CIRCULATION; EDEMA IN CARDIAC DECOMPENSATION

The edema found in cardiac decompensation is due to factors which obstruct the return of the venous blood to the heart. Secondarily there may be added to this direct circulatory effect interference with the function of the kidneys. The main problem which we have to consider concerns the way in which venous obstruction causes edema

and this leads back to the theories of lymph formation. The teaching of Ludwig, that filtration pressure in the blood-vessels is mainly responsible for the formation of lymph, was sustained especially by the experiments of Starling. In addition the latter assumed that in places of lowered blood pressure the excess of osmotic pressure in the blood-vessels, due to the presence of a surplus of protein in the blood, causes a return of the fluid into the capillaries. To these factors, present in a quantitatively abnormal manner, Starling attributed cardiac edema. Cohnheim emphasized as a further factor an injury of capillary walls due to malnutrition. According to these views then cardiac edema is due to the rise in capillary and venous pressure, and to the resulting increase in filtration combined with a lowered ability of the vessels to reabsorb the fluid, owing to the hydremic character of the blood which has become less potent osmotically. In addition the increased permeability of the injured vessels permits a greater amount of fluid to filter out of the blood-vessels. Those authors who attribute the transudation of fluid from the capillaries into the tissue mainly to an increase in intracapillary blood pressure, interpret likewise the microscopic changes observed in the frog circulation in cases of venous obstruction as due to filtration of fluid (Klemensiewicz); they point furthermore to the watery condition of the lymph in passive congestion and assume that, whether or not edema follows, increased filtration pressure depends upon the facilities which exist for the elimination of the excess fluid which has passed into the tissues. As to this latter condition, again mechanical factors play a preponderating rôle according to these conceptions. Wherever the tissue shows a dense structure, the fluid is pressed back primarily into the blood-vessels; only in loosely built tissue does an accumulation of fluid readily occur. Thus in the experiments of Ludwig and Thomas ligation of the plexus pampiniformis led to an edema of the loose tissue surrounding these veins. The lower eyelid likewise is a favorite seat for renal edema on account of the looseness of the structure of this tissue. In venous thrombosis and cirrhosis of the liver obstruction to the outflow of blood may also lead to edema through similar mechanisms.

While all these considerations suggest that such mechanical factors may play a part, still even several of the older experiments tend to

prove that other factors must be combined with increased filtration pressure if edema is to result. Thus arterial hyperemia due to vasomotor paralysis, when added to obstruction to the venous outflow, may produce edema, though either of these two procedures alone would prove ineffective. Cohnheim showed that the cutting of the cervical sympathetic nerve in the rabbit and a simultaneous tying of the large vein of the root of the ear will produce edema of the ear of the rabbit, while such an effect cannot be produced through a cutting of the sympathetic alone; a cutting of both the sympathetic and the auricular nerves, which increases the vasodilatation, will however also have this effect. Similarly a ligation of the femoral vein in the dog does not lead to edema, owing perhaps to the establishment of collateral channels of circulation; but if the tying off of the femoral vein is accompanied by a cutting of the sciatic nerve, the principal vasomotor nerve of the leg, edema will result.

On the other hand, there are facts which make it possible that even in cases in which variations in blood pressure, tissue pressure, and filtration were assumed to be the principal causes of an increased transudation, other factors, and especially variations in the permeability of the capillary wall, play an important rôle. Thus, for instance, the experiments of Asher and Boehm on the effect of adrenalin on transudation, suggest that filtration may play a more subordinate rôle than had been assumed, even in conditions in which mechanical factors suggested themselves primarily.

The more recent observations concerning the permeability of the capillaries, to which we referred in the preceding chapter, render it likewise very probable that while we cannot exclude the possibility that increase in blood pressure may be a factor in the surplus transudation of fluid into the tissue which leads to edema, an increased permeability of the capillaries, associated with their dilatation, may be a factor also, and an important one, in the formation of edema, even in cases in which the capillary blood pressure is increased.

It is assumed by many authors that the malnutrition of the capillary endothelia and of the surrounding connective tissue in cases of cardiac decompensation increases the permeability of the vessels for water, salts and even proteins, and that these substances thus accumulate in the interstitial tissue surrounding the capillaries. It

appears that non-protein nitrogen also is retained in the tissues in certain cases of severe cardiac decompensation accompanied by deficiencies in kidney function (O.Kleine). Such an injury of the capillary vessels might be due to a disturbance of the acid base equilibrium in the blood and tissue through a lack of oxygen. A lack of oxygen in the venous parts of the capillaries and in the veins may be produced in two ways: (1) through a deficient oxygenization of the blood in the lung, and (2) through an increased use of oxygen as a result of the slowing of the capillary circulation. Both play a part, in varying degrees, in different kinds of cardiac lesions, as especially Lundsgaard has shown in quantitative determinations. There may in addition be a deficiency in arterial oxygen, if the pulmonary gas exchange is very faulty (Harrop). To some extent this deficiency in the supply of oxygen is counteracted by an increased minute volume of inspired air. This factor as well as the increased elimination of oxygen from the capillaries may lead to an increase in basal metabolism in cases of cardiac decompensation (Peabody,Wentworth and Barker). Yet this compensatory process does not necessarily safeguard against a lack of oxygen in the venous component of the capillaries and deficient nutrition of certain capillary connective tissue areas might result, despite an increase in oxygen consumption. In addition a deficiency in proteins which has been recorded in the blood in cardiac decompensation might lead to malnutrition of the vessels and the surrounding tissues. While we have thus to take into account the possibility of injury to the vessel wall, yet the actual proof that these factors do cause abnormalities in the interchange of substances between vessels and surrounding tissue has so far to our knowledge not been given.

With the view that factors other than increased filtration pressure may play a part in the edema accompanying venous obstruction, the studies of Bolton agree as to the mechanism of cardiac edema, which he produced through partial constriction of the inferior vena cava. He finds that edema, which develops within a few hours after the onset of the obstruction, is independent of a rise in capillary pressure. It depends instead upon a venous and capillary congestion, accompanied by a distention of the capillary and venous channels and by a slowing of the blood flow. This leads to an increased transudation of fluid

from the vessels, which is accompanied by a diminished reabsorption; it is thus associated with an increased flow of lymph. In addition there develops a hydremic plethora in the vessels, due to an increased absorption of fluid at points of the circulatory system where the capillary pressure is lowered, and due also to secondary changes in the kidney function. This condition tends still further to increase the transudation of fluid and the amount of edema. The hydremic plethora is subsequently transformed into a true plethora in consequence of a new formation of erythrocytes. The edema may increase for a period of several weeks, but it disappears as soon as blood-vessel anastomoses have been established; the latter lead to a more rapid circulation of the blood and with the cessation of stagnation the increased transudation and the lowering of the absorption of fluid from the tissues into the blood come to an end. Bolton hesitates to assume that a structural damage is inflicted on the capillary walls as the result of malnutrition, considering the rapid improvement which takes place with improved circulation.

While the experimental procedures used by Bolton cause an acute venous obstruction, it is possible to produce experimentally in the rabbit a state in which the heart acts normally under the usual conditions, but an inferiority of the heart action becomes apparent as soon as excess work is required. Fleisher and Loeb produced myocarditic lesions in rabbits by a single intravenous injection of a combination of adrenalin and spartein or caffeine. This procedure is followed in a considerable number of animals by structural alterations especially near the auriculo-ventricular groove, and, as Christian, Smith and Walker have shown, it may even lead to endocardial alterations. Such a heart works apparently well under usual conditions, but if intravenous infusions of solutions of sodium chloride or of a combination of sodium and calcium are made, the heart is not equal to its task; the blood pressure is lowered, more fluid is retained within the vessels, and, as the result of these circulatory changes, the amount of urine secreted is diminished. On the other hand the quantity of peritoneal transudate and of intestinal fluid produced is not thereby noticeably altered. It seems then that the formation of intestinal fluid is to a greater extent independent of vascular changes than the formation of urine. The further experiments of Fleisher and Loeb

on the inability of adrenalin to affect the intestinal fluid are in agreement with these results. While therefore under these experimental conditions the heart lesion does as yet not lead to edema, still it permits us to imitate experimentally the circulatory conditions which prepare the way for the development of edema. It seems, however, that in animals in which myocarditis has thus been produced experimentally, the liability to the formation of pulmonary edema is somewhat increased. We believe that this method may prove useful in the further analysis of cardiac edema.

In addition to an increased transudation a decreased absorption of fluid from the tissue spaces plays a part in the development of cardiac edema. Thus in persons suffering from decompensated heart disease and subsequent edema, Reichel observed a delay in the absorption of fluid injected subcutaneously. F. Kauffmann found a delay in the absorption of injected fluid from the subcutaneous tissue even in patients suffering from compensated heart disease without a visible edema. This author furthermore states that in patients who are in a state of pre-edema, and in whom a retardation in the excretion of fluid and a retention of fluid in the intercellular spaces, especially of the lower extremities, occur, although this retention is not yet visible to the naked eye, elevation of the lower extremities causes an increased elimination of the fluid and an increased diuresis. In such pre-edematous cases the weakening of the circulation leads to a slowing of the blood flow through the lower extremities, with both a subsequent retardation in the absorption of fluid into the capillaries from the subcutaneous spaces and an increased elimination of fluid from the blood into the tissue spaces. An improvement in the circulatory conditions counteracts this effect. If, on the other hand, edema is once well developed, this procedure ceases to be effective.

We may conclude that an increase in the amount of interstitial fluid, a condition of pre-edema or of latent edema, exists even in certain cases of apparently compensated heart disease; but the movement of water from the capillaries to the surrounding fluid is here quantitatively weaker and thus there results merely an invisible edema. We are accustomed to conceive of edema a well fixed entity. Instead we have probably to deal with a process of a continuously increasing character. When a certain limit has been reached in this abnormal

process, we speak of edema. This consideration applies in all probability to all kinds of edema, including those of a renal origin.

It holds also in conditions in which a local slowing of the circulation exists as, for instance, in case of varicose veins in the lower extremities. Here too all degrees of retention of fluid in the interstices of the connective tissue exist from apparent normality to distinct local edema in the dependent parts of the body. In many other conditions a latent retention of water exists; it has been observed in pneumonia (Schwartz). Yet to our knowledge no systematic attempt has been made so far to analyse these minor disturbances in the retention of water and salts.

A somewhat related condition, in which an experimentally produced obstruction to the blood flow led to a retardation in the absorption of fluid and to subsequent edema, seems to have been realized by Galeotti, who injected into a dog intravenously a hypertonic solution of sodium chloride or sugar after the crural vein had previously been ligated. While under normal conditions the hypertonic transudate which enters the tissue spaces from the blood-vessel would rapidly be absorbed, absorption in such a case is retarded as a result of the circulatory disturbances. Consequently the hypertonic transudate remains for a longer period in the tissue spaces, attracts fluid from the surrounding sources of water supply, and thus edema develops. Whether, as Galeotti suggests, an increased transudation under the influence of the hypertonic salt solution is the cause of edema in this case is doubtful. This experiment is also instructive as a further illustration of the fact that several factors, which, when acting singly, are ineffective, may when acting in combination be sufficient to call forth edema. It is then probable that associated with the increased transudation in heart disease there is a retardation in absorption responsible for the development of edema.

Not only do we find a delay in the absorption of fluid but also a retention of sodium chloride in cases of cardiac edema and in this respect the latter resembles renal edema. Vaquez and Digne observed a retarded elimination of sodium chloride even in cases of compensated heart disease. Barantschik likewise found a retardation in the excretion of an excess of NaCl given with the food, a retardation which is independent of a kidney lesion. If an excess of sodium chloride

is given, without a corresponding amount of water, a dry retention of sodium chloride may occur with or without an accompanying edema. Such a dry retention may also be followed by edema and a subsequent excess elimination of NaCl, which surpasses the amount of this salt usually eliminated in a corresponding quantity of edematous fluids.

Strauss states that a hydremia, as determined by the refractometer, occurs only in severe cases of cardiac decompensation. Veil also and other authors find occasionally a hydremic plethora in cardiac decompensation. According to Beckmann the condition which we find in the blood depends upon the degree of saturation of the tissues with water. If the tissues have become saturated with water, a back flow of water to the blood takes place and thus the blood becomes more diluted. In later stages of the disease, on the other hand, sometimes an inspissation of the blood has been observed (Loeper and Cheray and others). Heineke finds that if diuresis takes place in cases of cardiac edema, first a dilution of the blood occurs and subsequently an increased concentration. Part of the edematous fluid is discharged through increased perspiration. These observations suggest that the state of the tissues plays a certain rôle in cardiac edema. In the same direction perhaps points the following experiment of Nonnenbruch: In passive congestion and edema of cardiac origin, water given by mouth is retained, but given intravenously it is excreted—a condition which is the reverse of that found in normal dogs. According to Nonnenbruch this result indicates that the kidney is able to excrete water and sodium chloride and that it merely fails to do so because the tissues retain the fluid. It might, however, be that in cases of cardiac decompensation water given intravenously is excreted more rapidly, because in this case the constitution of the blood is temporarily changed much more rapidly than if the fluid is given by mouth. In the latter case the alteration in the composition of the blood might be too slight to act as a stimulus. As to the existence of plethora, the findings of Bock seem to contradict the conclusions of those authors which assume the existence of a real plethora in heart disease. With the vital red method Bock noticed no change in the quantity of the blood plasma in heart disease.

On the whole the concentration of sodium chloride in the blood in cases of cardiac decompensation and edema seems often to be low (Veil, V. Monakow, Bauer). Probably this substance enters the transudate and the tissues and is here retained; in other cases, however, its concentration in the blood may be normal. Veil states that a hyperchloremia, similar to that found in certain kidney diseases, does not occur in heart disease. Yet it seems that certain variations in the sodium chloride content of the blood do occur in heart disease and that in some cases the concentration of this substance in the blood may be increased, especially at the time when the edema begins to form, or at the time of its disappearance.

A salt free diet may lead to a dilution of the blood, owing to the movement of the water from the tissues to the blood and thus to an elimination of the fluid which may take place partly through other channels than the kidney (Heineke). But while changes in the elimination and distribution of sodium chloride are in cardiac edema on the whole similar to whose in nephritic edema, the significance of these factors does not seem to be so marked in cases of cardiac as in cases of renal edema. In the former withdrawal of sodium chloride from the diet does not lead to so rapid a discharge of the edema as in the latter, nor addition of this substance to so marked an increase in the quantity of the retained fluid (Magnus-Levy).

In addition to abnormalities in the distribution of sodium chloride, there may also be a retention of other substances in cases of cardiac decompensation. Thus an increase in the non-protein nitrogen in the blood is found, although only in extreme cases of cardiac decompensation, or when a decompensation of a medium intensity has lasted for a longer period of time, a condition which usually is associated with oliguria (Otto Klein); it may be the latter which is mainly responsible for this increase of non-protein nitrogen.

Summary

Dilatation of the capillaries and veins due to the faulty functioning of the circulation is the principal cause of the increased transudation and the subsequent edema in cardiac decompensation, but there may perhaps be in addition an increased filtration pressure responsible

for these results. The vascular dilatation is apparently followed by an increased permeability of the capilllaries and by a movement of sodium chloride and water in the direction from the blood to the tissues. Retention of sodium chloride plays a rôle also in the case of cardiac edema, although it is a smaller one than in the case of renal edema. In certain stages of cardiac edema a hydremia seems to occur. As to the occurrence of a true plethora, the statements are contradictory. In addition to the increased transudation, there is a delayed absorption and an alteration in the relations determining the exchange of fluid between tissues and blood-vessels. Experimentally produced myocarditic lesions may give rise to a lowering of blood pressure and a diminution in the amount of urine under certain conditions, but so far it has not been possible to influence by this experimental method the amount of edematous fluid.

IIIa. DECREASED EXTRAVASCULAR PRESSURE AS CAUSE OF EDEMA

In certain cases a localized edema is caused by an absorption of tissue provided the cavity thus produced is not filled in by the surrounding tissues. Thus atrophy of the brain, which is surrounded by a bony, unyielding capsule, may lead to edema; atrophy of fat may in certain cases have a similar effect. The transitory edema following cupping represents an acute condition of the same character.

In these cases a mechanical factor, a disparity between intravascular and tissue pressure, seems to be the cause of the edema.

IV. THE INFLUENCE OF ADRENALIN ON THE FORMATION AND ABSORPTION OF TRANSUDATES

In order to separate the various factors which may be responsible for edema, it is not without interest to study the effect of substances with some well defined physiological actions like adrenalin in the development of edema. Adrenalin causes a constriction of arteries and capillaries and raises the blood pressure. In small doses it may dilate the capillaries; furthermore in certain organs the action of adrenalin on the blood-vessels seems to be generally that of dilatation. It retards the absorption of certain substances parenterally introduced and their elimination into the blood-vessels (Exner, Meltzer and Auer).

In recent experiments Embden and his collaborators (Kauffmann, Lange) found that adrenalin retards the exchange of substances through a membrane consisting of frog skin as well as the entrance of substances into the muscle and the passing of substances out of the muscle. In this case adrenalin affects the membrane lining the muscle fibers in a manner similar to frog-skin and blood-vessel wall. The effect of adrenalin in diminishing the permeability of membranes seems therefore a general effect and in this respect it resembles calcium chloride. In both of these substances the diminution in permeability of membranes goes hand in hand with a contraction, provided the membrane contains contractile elements. It is probable that to this effect in decreasing the permeability of the capillaries is due the retarding influence which adrenalin may exert on the development of inflammatory edema, as for instance, the edema caused through instillation of mustard oil in the conjunctiva of rabbits.

If injected in a large quantity intravenously into rabbits, adrenalin causes an acute edema of the lungs. On the other hand, the slow, continuous intravenous injection, extending over a period of twenty minutes, leads to a rise in blood pressure in the somatic as well as in the splanchnic areas; it impedes the circulation in the liver and causes an increased lymph flow (Bainbridge, Trevan, Erlanger and Gasser). Hess, Erb and Lamson found that an injection of a larger amount of adrenalin is followed by passing of fluid out of the vessels; the blood is thus made more concentrated.

It is usually assumed that this change in composition of the blood is due to a filtration process, the result of the increase in blood pressure under the influence of adrenalin. In accordance with the findings of Bainbridge and Trevan, Lamson refers it to the obstruction which develops in the capillaries of the liver after injection of adrenalin. This is supposed to lead to an increased transudation of fluid into the lymph vessels of the liver. On the other hand in a recent study F. O. Hess finds that following injection of adrenalin, the number of erythrocytes is increased only in the arterial, but not in the capillary blood. He is therefore inclined to attribute the increase in the number of red corpuscles not to a movement of fluid out of the blood-vessels, but to a mechanical alteration in the distribution of the erythrocytes within different parts of the vascular system. Asher and Böhm

attribute the alteration in the composition of blood to an increase in organ activity caused by adrenalin. They are led to this conclusion because they find that an increase in blood pressure caused by mechanical measures does not result in an increase in concentration of the blood, an observation which agrees with the results of Lamson.

Fleisher and Loeb studied the effect of an addition of very small amounts of adrenalin to a solution of sodium chloride to which had been added a certain proportion of calcium chloride, the adrenalin flowing continuously into the jugular vein of a rabbit during a period extending over several hours. Under such conditions adrenalin leads to a continuous rise in blood pressure which lasts several hours. Only towards the end of the experiment a steep fall in blood pressure occurs, if calcium chloride has been added to the fluid, while with a pure solution of sodium chloride the blood pressure remains elevated throughout the experiment. The apparent pressing out of fluid from the vessels, which is noticeable after application of adrenalin over shorter periods of time, is not observed under these conditions. A certain increase in the concentration of the blood occurs, however, if adrenalin is injected intravenously in repeated doses, or if it is injected intraperitoneally together with a solution of sodium chloride; under such conditions a larger amount of adrenalin enters the blood-vessels in a unit of time than when this substance flows in continuously in very small quantities; if it is injected by the latter method through the jugular vein mixed with a solution of sodium chloride, it increases the amount of urine, leaves unchanged or diminishes the amount of intestinal fluid and increases the amount of peritoneal transudate. As far as the formation of urine is concerned, adrenalin and calcium chloride act antagonistically, but the effect of calcium chloride proves stronger in a mixture of sodium chloride, calcium chloride and adrenalin, and the amount of urine is diminished, but is still larger than if the calcium chloride and sodium chloride alone are used. The lowered secretion of urine results under those conditions notwithstanding the continued rise in blood pressure. The diminution of the intestinal fluid, which occurs under the influence of calcium chloride alone, is not markedly affected through the admixture of adrenalin. As to formation of peritoneal transudate, a summation of the effects of calcium chloride and adrenalin takes place and the amount of fluid

eliminated into the peritoneal cavity under those conditions is much increased. We find thus a tendency of adrenalin to increase the amount of fluid eliminated either into the peritoneal cavity or through the kidney and these effects run parallel to the rise in blood pressure caused by adrenalin. This increase in peritoneal transudation persists even in nephrectomized animals, and it is therefore not dependent on the function of the kidney.

Equally definite is the effect of adrenalin administered intraperitoneally or intravenously in increasing the absorption of fluid from the peritoneal cavity (Fleisher and Loeb, A. J. Clark). This is contrary to what might have been expected considering the experiments of Exner, Meltzer and Auer, who found that adrenalin retards the movement of substances through capillaries. This increase in absorption of peritoneal fluid is independent of the osmotic pressure of the fluid injected intraperitoneally. At the same time adrenalin augments also the absorption of sodium chloride from the peritoneal cavity. In case distilled water is injected intraperitoneally adrenalin diminishes the passage of sodium chloride from the blood into the peritoneal cavity and the sodium chloride concentration of the peritoneal fluid. This agrees also with the observations of Achard and Caillard in guinea pigs. In some cases adrenalin increases not only the total amount of sodium chloride which is absorbed from the peritoneal cavity, but it increases the absorption of this substance relatively more than that of water, and there may thus still be an increased absorption of sodium chloride from the peritoneal cavity in cases in which the absorption of water is no longer increased through adrenalin, as in nephrectomized animals or in animals which have been injected with uranium nitrate three days previously. As early as one day after administration of uranium nitrate, on the other hand, the absorption of fluid from the peritoneal cavity and the secretion of urine are still increased by adrenalin. We can explain the effect of adrenalin on absorption of fluid through its effect on the osmotic pressure of the blood, which we found raised under the conditions of our experiments, following administration of this substance. This increase in osmotic pressure leads to an increased absorption of water from the peritoneal cavity. When on the other hand the osmotic pressure of the blood is already raised previous to the injection of

adrenalin, as is the case in animals nephrectomized or operated upon otherwise, or injected with uranium nitrate three days previously, adrenalin no longer influences the absorption of fluid from the peritoneal cavity, but it may still accelerate the absorption of sodium chloride. At the same time there seems to be a connection between the action of adrenalin on the kidney function on the one hand, and its effect on the absorption of transudates on the other hand. The influence of adrenalin on the passage of water and dissolved substances from the blood-vessels into the tissues may also be a factor which determines the effect of adrenalin on the distribution of fluid in the body. The increase in the amount of ascitic fluid under the influence of intravenously injected adrenalin, is explained probably by the peculiar change produced in the circulation of the liver, by this substance (Bainbridge and Trevan, Erlanger and Gasser). There are certain similarities existing between the effects of calcium chloride and adrenalin; both retard the passage of substances through membranes and cause a contraction of blood-vessels, if used in certain concentrations, and both may prevent certain inflammatory symptoms; at the same time these substances increase the amount of fluid eliminated into the peritoneal cavity after intravenous injection of salt solutions.

Summary

We find adrenalin a substance which affects in a definite way the distribution of edematous fluid and of sodium chloride. We have shown that at least a part of these effects is secondary to osmotic changes which are produced by adrenalin. It has furthermore been shown that adrenalin affects the permeability of membranes. How far in addition localized changes in blood pressure play a part in this process, cannot be stated definitely at the present time. It is however of interest that two substances as diverse as adrenalin and calcium chloride show similar effects on the distribution of fluid and dissolved substances; both decrease the permeability of different kinds of membranes for water and lead to a contraction of vessels, if used in certain concentration, and both increase at the same time the amount of ascitic fluid.

V. EXPERIMENTAL EDEMA IN EMBRYOS AND IN ADULT AMPHIBIA

McClure produced edema in frog larvae by exposing the embryos at an early stage of development to various injurious influences which prevented the normal formation of the pronephros tubules. In consequence of this interference the fluid which otherwise would have left the body as glomerular filtrate was retained in the body cavities. Similar conditions can be produced through bilateral extirpation of the pronephros in amphibian larvae (Swingle, Howland). Unilateral removal does not seem to have the same effect. In adult frogs also ligature of the ureters or cloaca produces edema (Overton). In these cases edema seems to affect mainly the large body cavities, but to a less extent also the subcutaneous tissue. Here it starts around the skin wound and gradually extends into the anterior region of the body. Recently E. Pohle confirmed the results of Overton in adult frogs. Extirpation of the kidney produces an increase in the amount of peritoneal fluid; it does not cause, however, a filling of the lymph sacs nor edema of the interstitial tissue of the skin.

E. L. and E. R. Clark showed that while interference with the blood circulation leads mainly to a collection of fluid in the body cavities, procedures which interfere with the development or function of the lymphatics in amphibia produce a much more generalized edema. The same effect of the lymphatics can be observed in chick embryos. The elimination of fluid in these organisms appears therefore to be effected principally through the lymphatics.

In edematous larvae the tissues proper in which the interstices are filled with fluid show signs of degeneration; they become vacuolar (Howland). This is presumably due to a secondary interference with the nourishment of the edematous parts of the body. It is very probable that the edema thus produced experimentally in larvae is to be attributed to mechanical factors, which lead to an insufficient elimination of fluid and the latter is then held back in the skin or in the body cavities.

Toxic conditions also may lead to edema in amphibian larvae; this has, for instance, been observed in salamanders which have been fed with thymus gland (Uhlenhuth). In this case circulatory disturbances also may possibly play a part, inasmuch as a slowing of the circulation is noticeable in larvae brought up on such a diet.

We see then that it is possible to produce edema in organisms representing somewhat more primitive stages of ontogenetic or phylogenetic development, by relatively simple means which interfere with the elimination of fluid. This is perhaps due to a greater intake of fluid in proportion to the body volume; or possibly the lack of certain regulatory mechanisms which come into play in higher forms may be responsible for this result.

VI. OBSTRUCTION TO THE LYMPHATIC CIRCULATION AS A CAUSE OF EDEMA; LOCAL DIFFERENCES IN THE FORMATION AND ELIMINATION OF INTERSTITIAL FLUID

In the preceding chapter we referred to the experiments of E. L. and E. R. Clark, who showed that procedures which interfere with the development or function of the lymphatics in amphibian larvae, produce a much more generalized edema than does interference with the blood circulation. Similar results have been obtained in chick embryos. These observations suggest that obstruction of the circulation of lymph may quite generally be a factor in the origin of edema, but that in higher organisms compensatory mechanisms may retard or prevent its appearance.

Older experiments, in which the effect of obstruction of the lymphatic circulation as to the production of edema was tested, gave contradictory results. While Cohnheim was not able thus to produce edema, according to Boddaert (cited by Meltzer) edema may result provided the obstruction to the lymphatic outflow is complete. The latter seems the more probable conclusion.

There are also more recent observations which favor this conclusion. Thus Volhard produced edema in the legs of frogs, in which arterial and venous circulation was maintained, while the lymphatic circulation had been obstructed through compression. This author explains this edema as due to interference with the return flow of lymph. Chronic edema may follow occlusion of lymph channels by filaria or their ova. This obstruction to the lymph flow and the resulting edema often lead in addition to connective tissue proliferation and elephantiasis. Opie observed, in cantharidin poisoning, edema of the liver, which he attributed to occlusion of the lymph

sinuses in lymph glands serving as channels for the hepatic lymph. In a case in which a carcinoma of the stomach caused widespread embolic metastases in the lymphatic vessels, which obstructed the lymph flow, extensive edema developed, at a time when the blood circulation was still good and cachexia absent (Schierge). We may assume that the obstruction to the outflow of chyle and lymph proper forced these fluids back into the serous cavities and interstitial tissue. Whether or not in order to obtain such positive results secondary factors must be active, in addition to this preliminary obstruction to the circulation of the lymph, cannot be definitely stated at the present time. If Cohnheim was unable to produce edema through ligation of lymphatics in the dog, it is possible that in these experiments the obstruction to the lymph flow had been incomplete and that the activity of the venous capillaries compensated for the deficiency in the effectiveness of the lymphatics.

In addition to a direct influence on the formation of edema, obstruction to the lymphatic circulation may render more difficult or prevent the absorption and elimination of edematous fluid, which has accumulated as the result of other pathological conditions; thus it may come about that a partial elimination of the edematous fluid by therapeutic means may be followed by a more complete elimination, owing to the freeing of the lymph circulation from the obstruction which was caused by the pressure of the edematous fluid.

In this connection we may state that it is believed that the blood-vessels represent the most important channels of absorption of the interstitial fluid. There is however reason for assuming that the lymph vessels also may participate in this process of absorption, although the extent of this participation does not seem to be definitely known at the present time.

The experiments on edema in embryos and in adult frogs, which we mentioned, indicate that here edema can be produced under conditions which would not lead to edema in normal mammals. There exist thus differences between different kinds of organisms in the readiness with which edema develops. But certain variations we find even in the mammalian organism, in the readiness of different tissues to become edematous. Thus while in general plethoric hydremia produced through intravenous injection of sodium chloride

solution does not produce edema of the interstitial tissue (Cohnheim and Lichtheim), it may have this effect in the connective tissue around the salivary glands, pancreas and the large vessels of the neck. This localized predisposition to edema does not depend upon organ activity, because it is also found around denervated and inactive glands (Wertheimer and Battez). In all probability it is caused by structural peculiarities which exist in the relations between the vessels and the connective tissue of various regions. Furthermore, it has been found that in the case of edema surrounding the salivary gland, for instance, that the activity of the gland itself may lead to a withdrawal of water from the interstitial edematous fluid and to its transport into the gland duct. This does not however occur if the gland has been made inactive through denervation or through the application of atropin (Wertheimer and Battez). There may be thus a third way of direct elimination of edematous fluid from the tissue spaces, through certain glands in addition to the usual route through blood and lymph channels. The choroid plexus may perhaps act in a similar way.

VII. EDEMA OF THE LUNG

The circulation and structure of the lung show certain peculiarities which make advisable a separate discussion of edema of this organ. There is an anatomical difference between pulmonary and the ordinary interstitial edema. In the former the edematous fluid not only fills the connective tissue spaces of the lung tissue, but usually also the alveolar air spaces which are lined by epithelium. In addition there seems to occur a pseudo-edema of the lung, due to a hypersecretion of bronchial and tracheal glands, which is followed by a movement of the secreted fluid into the air spaces; however, this is an effect which we do not need to consider. The real edema of the lung may be induced by many conditions which do not greatly differ from those found in other regions. There are, however, certain causes of edema which are peculiar to the lung, the main ones being as follows: (*a*) The terminal edema of various diseases may be limited to the lung. (*b*) Acute pulmonary edema may result from the inhalation of certain gases and also from certain other substances (like iodine, morphine, muscarine), even if they reach the lung merely by way of the circula-

tion. (*c*) Acute pulmonary edema may follow a sudden occlusion of the air spaces due apparently to a mechanical sucking of fluid from the circulation into the air spaces. (*d*) Edema of the lung and pleura may follow inflammation, here as elsewhere. (*e*) Edema restricted to the lung alone may occur in diseases of the circulatory system and of the kidneys. (*f*) It has been found furthermore in some skin affections, which are associated with an abnormal permeability of the capillaries, and lastly (*g*) pulmonary edema has been observed in certain nervous diseases.

Experimentally the main interest has attached to attempts to produce pulmonary edema through interferences with the circulation in the lung and through inhalation of poisonous gases. Welch obstructed the pulmonary circulation by various means and was able to produce edema of the lung only when obstruction to the outflow of blood from the lung tissue became very intense.

It is evident that in the usual clinical cases of pulmonary edema such an intense obstruction to the flow of blood does not exist. A similar condition however can be experimentally produced through intravenous injection of adrenalin in rabbits. We shall refer to this kind of edema again. Welch assumed that even without such a marked degree of obstruction, pulmonary edema may be caused by a disproportion between the working power of the left and right ventricle, in consequence of which the left heart is unable to expel in a unit of time as large a quantity of blood as is expelled by the right heart, provided the resistance to the movement of blood in the peripheral circulation remains unchanged. As Meltzer observes, the edema following intravenous injection of a large dose of adrenalin is in all probability due to a great rise in systemic blood pressure, which obstructs the outflow of blood from the left heart, while that from the right ventricle continues. It would therefore represent an extreme case of a disproportion between the working of the two sides of the heart. With this interpretation of the acute pulmonary edema produced in rabbits through adrenalin, the finding of Schaefer and Lun is in agreement, according to which adrenalin causes a much more significant rise in the systemic than in the pulmonary arterial pressure. Miller and Mathews point out that the pulmonary edema consequent upon administration of iodides also conforms to Welch's explanation,

and Hallion and Nepper apply it likewise to the edema following over-exertion and excitement, with subsequent rise in blood pressure, in cases of nephritis and insufficiency of the left ventricle. According to Matsuoka in beri-beri, where pulmonary edema may occur, an early weakening of the left ventricle with hypertrophy of the right ventricle may be observed. Under these conditions the lungs are not pale, as assumed by Sahli, but on the contrary congested. This edema is therefore again obstructive in character. In addition there may be a constriction of the pulmonary and bronchial arteries which leads to a regurgitation of the blood into the lung capillaries. Similarly this author interprets the terminal pulmonary edema generally as obstructive and mechanical in character. Therefore in the agonal edema red corpuscles are usually mixed with the transudate.

This interpretation of the origin of pulmonary edema is also in agreement with experiments of Modrakowski and Matsuoka, in which they perfused the isolated lungs, or Starling's lung and heart preparation, and found that the occurrence of edema depends upon such a relation between the pressure in the inflowing and outflowing fluid that an increased capillary pressure and congestion of fluid in the capillaries result. We may conclude that the mechanical factors which lead to edema of the lung cause a capillary congestion of the lung. An actual paralysis or impairment of the left ventricle may not be necessary for this purpose; a very efficient working right ventricle may be able to produce an edema of the lung, notwithstanding the continued pumping of the left ventricle, especially if the latter works against increased resistance.

However, while the best evidence favors the conclusion that passive congestion in the lung may lead to pulmonary edema, it seems that, on the whole, the lung tissue is relatively resistant to those effects of obstruction and that in many cases circulatory deficiencies are not followed by edema. In certain cases of pulmonary edema no signs of passive congestion are noticeable according to Sahli.

In many cases of chronic cardiac decompensation, with passive congestion of the lung, pulmonary edema does not occur. Either the back-pressure of the blood must be very great or the tissues must be relatively little resistant, before edema results. Such a low degree of tissue resistance plays apparently a certain rôle in pulmonary

edema in the rabbit. On the other hand it is possible that secondary tissue changes, which occur in the course of passive congestion in the lung, may in certain cases prevent edema, yet it may very well be that even in passive congestion, if edema should occur, it is not so much the mechanical factor of increased back-pressure of the blood which is responsible for this result as the change in the tissue of the lung. Thus Lubarsch suggests changes caused by bacterial infection as a cause of pulmonary edema. Modrakowski likewise states that in diseased lungs, edema occurs more readily than in normal lungs, and that ammonia mixed with the circulating fluid causes edema independently of mechanical factors. Fleisher, Hoyt and Loeb observed that a solution of calcium chloride, approximately isotonic with a 0.85 per cent solution of sodium chloride, added in the proportion of one volume of calcium chloride to five volumes of sodium chloride solution, almost doubles the frequence of pulmonary edema, and Carrion and Hallion and others found that hypertonic sodium chloride solutions, injected intravenously, are more liable to cause edema in the lung and elsewhere than isotonic solutions. Roger and Garnier produced edema of the lung in rabbits in which they injected intravenously sodium chloride solution to which gum or gelatin had been added. In this case the pulmonary edema was presumably due to the increase in the quantity and viscosity of fluid circulating in the vessels; there was neither a rise in the blood pressure nor an impairment of the left as compared with the right ventricle under these conditions. Klemensiewicz states that old serum, used in perfusing lungs, more readily causes pulmonary edema than fresh serum. However, the most convincing example of edema of the lung due to the alteration of the lung tissue is that caused by inhalation of poisonous gases like chlorine and phosgen. Though E. Schaefer, and following him Weller, assume that even in this case mechanical factors play a considerable rôle, the chlorine changing the viscosity of the blood and leading to stasis and thrombosis in the lung and elsewhere. L. Hill as well as Laqueur and Magnus have shown that these gases cause edema of the lung primarily by altering the tissue, increasing the permeability of the vessels and injuring the endothelial lining of the alveoli. Hill especially has proven that chlorine gas may cause edema in concentrations which do not yet alter the blood in such a way that stasis occurs.

We find thus good evidence for assuming that changes in the permeability of the pulmonary capillaries and concomitant alteration of the alveolar epithelium may lead to pulmonary edema, but we may go even further and consider whether the edema caused through mechanical obstruction in the circulation is not likewise in certain cases due to an increase in the permeability of the capillaries. Reasons similar to those which apply to general edema in cardiac decompensation, make it probable that this factor is also of importance in pulmonary edema.

Considerations of a like nature apply furthermore in all probability to the pulmonary edema observed by F. Kraus in cats, in which a double vagotomy had been carried out; here intravenous injection of a normal salt solution caused edema, while in normal animals the salt solution was without effect; however, the manner in which the cutting of the vagus alters the tissue in this case is uncertain.

If we summarize these observations, we may conclude that in all probability edema of the lung is produced through an increase in the permeability of the capillaries, which is the result of their dilatation. This dilatation may be brought about through mechancial obstruction within the circulation, or it may be brought about through the action of irritating substances and the edema may, in this latter case, be increased through the destructive effect of these substances on the tissues.

If the increased permeability is produced through mechanical interference with the circulation, blood pressure effects may be added to the changes in the permeability of the vessels and may thus increase the edema. In certain cases when the mechanical obstruction is very intense and especially if the tissue possesses normally a small degree of resistance, the pressure itself may suffice to cause edema of the lung.

Pulmonary edema is also of interest in another respect; it clearly demonstrates that we have to deal in edema with a pressing out of fluid from the vessels rather than with an attraction of fluid by the colloids of the tissues surrounding the vessels, and, as Hill observed, large amounts of fluid can be found in the interstices around the blood vessels.

We may assume that as in other kinds of edema, so also in pulmonary edema, we have to deal with changes which lead to a pressing out of the fluid from the blood-vessels into the lung tissue proper and which at the same time render more difficult the movement of fluid in the opposite direction. Whenever these changes are lacking an abnormal distribution of fluid is corrected apparently without much difficulty, as for instance, in the experiments of Winternitz who found that fluid injected intratracheally into the lungs of dogs is soon absorbed and that such an injection does not lead to a real pulmonary edema.

As to the treatment of pulmonary edema, Haven Emerson found that artificial respiration can save the life of cats in which, following injection of large doses of adrenalin, pulmonary edema is beginning to develop. This author believes that the artificial respiration causes a flow of blood to the left ventricle and prevents its stagnation in the lungs. L. Hill likewise observed the beneficial effect of artificial respiration in pulmonary edema caused by chlorine gas. He attributes it however to the pressing out of fluid from the alveoli.

Laqueur and Magnus found that in cats double vagotomy prevents or at least decreases the intensity of edema of the lung which develops after inhalation of phosgen gas. They believe this effect to be due to the interference with the transmission of sensory stimuli from the lung caused by this process. This observation would therefore confirm the importance of sensory stimuli in the development of inflammatory edema. These authors furthermore succeeded in lowering the mortality from phosgen gas poisoning through the subcutaneous injection of calcium salts previous to the development of pulmonary edema. Thus in a certain number of cases the intensity of the edema was diminished and the mortality fell from 88 to 55 per cent. In agreement with Chiari and Januschke they assume that calcium changes the texture of the tissue in such a way that the walls of the lungs become less permeable to fluid. It may, however, be possible that the effect of this treatment is due to a contraction of the pulmonary vessels and that calcium chloride thus decreases the permeability of the latter. On the other hand, Boycott, who had carried out similar experiments on the action of calcium salts on the escape of fluid from the pulmonary vessels following the use of poison gas in goats, did not obtain beneficial results, or at least the effects of this

mode of treatment were not striking. As we have stated above, addition of a sufficient amount of calcium chloride to a solution of sodium chloride increases rather than diminishes the incidence of edema of the lung after intravenous injection of this fluid. Under these conditions calcium chloride evidently does not lead to a constriction of the vessels nor to a decrease in the permeability of the tissues.

A more marked effect in the prevention of pulmonary edema can be obtained in rabbits through intravenous injection of a considerable quantity of a 25 per cent solution of glucose, soon after the application of the phosgen gas. Hypertonic solutions of sodium chloride on the other hand do not have this influence in the rabbit and in the cat they may even increase the pulmonary edema, in accordance with the observations cited above. While thus prevention of edema is possible in rabbits, in cats even a 25 per cent solution of glucose is without effect. We may assume that in the case of rabbits the positive results are due to osmosis, water being withdrawn from the walls of the blood-vessels and tissues which are thus made less permeable to the plasma; in addition a withdrawal of fluid from the interstices and alveoli of the lung tissue may possibly occur. In contrast to these positive results, Erlanger and Gasser did not obtain noticeable results from the injection of hypertonic gum acacia solution in edema of the lung caused by inhalation of poisonous gas. They attribute this failure to changes in the capillaries caused by the gas, which lead to an increased permeability of the vessels. If the vessels act like a sieve an increase in the osmotic pressure inside the vessels can be of little avail.

VIIa. ON A MECHANICAL FACTOR IN THE DEVELOPMENT OF EDEMA IN THE PLEURAL CAVITY

In the course of pneumonia due to hemolytic streptococci, pleural exudate may develop very rapidly. Through experiments performed in vitro with excised lung, in which broncho-pneumonia or edema was present previous to excision, Graham found that at the end of expiration much fluid is squeezed out from the tissue into the pleural cavity, and that consequently without respiratory movements the amount of inflammatory pleural exudate remains much smaller. Mechani-

cal factors of a similar kind may also influence the amount of edematous fluid in diseased individuals under certain conditions; fluid may perhaps be squeezed either into the pleural cavity or into the lung vesicles; and it is thus also conceivable that the movements of the diaphragm and of the intestines may increase the ascitic fluid in some cases.

VIII. EDEMA OF THE BRAIN

Edema of the brain is, in the majority of cases, due either to circulatory disturbances or to inflammatory alterations of the blood-vessels and tissues. In principle it does not differ from circulatory or inflammatory edema elsewhere, as far as its development is concerned. It owes certain peculiarities to the anatomic relation between subarachnoid space, ventricles of the brain, and the lymph vessels, which show a characteristic arrangement, and also to the fact that the brain is enclosed in a resistant bony capsule; furthermore the soft consistence of the nerve tissue proper is of importance in this connection. As far as we are aware no important additions to our knowledge as to the origin of edema of the brain have been made in recent years. On the other hand some interesting recent contributions indicate that it is possible to modify the intensity of the pressure exerted by the cerebrospinal and interstitial fluid in the brain and thus possibly to prevent or at least to diminish edema of the brain in certain cases.

The investigations of Weed and McKibben have shown that it is possible to influence the volume of the brain and the pressure exerted by the cerebrospinal fluid through intravenous injections of hypertonic salt solutions or distilled water. The former diminishes the brain volume and the pressure of the cerebrospinal fluid, while the latter increases both. Hypertonic solutions of glucose are apparently less effective in this respect. According to Foley and Putnam the same results can be produced through administration of hypertonic salt solutions or of water by mouth or rectum. The changes thus produced may last as long as twelve hours or somewhat longer following the injection; but a return to the normal condition occurs before the end of the second day.

Sachs and Malone undertook the application of these procedures to the treatment of pathological conditions of the brain, caused through

an excess pressure, such as is found in brain tumor or in edema of the brain. Experimentally they succeeded through injection of hypertonic salt solution in dogs in reducing the pressure in the skull which had been raised by experimental means; similar effects were obtained in some patients suffering from abnormal pressure.

Weed and McKibben examined microscopically the brain of cats in which they had produced experimentally changes in the water content. It seems that the changes in the osmotic pressure of the blood affect the behavior of the fluid both in the intercellular spaces surrounding the cells, as well as in the cells proper, causing these latter either to shrink or to expand.

These results agree with the effects of hypertonic solutions obtained by Ellinger in the prevention of pulmonary edema and with the observation of Gayda, who likewise varied the extent of general edema by osmotic factors. We see thus a close parallelism between the experimental procedures used for the prevention or diminution of pulmonary edema and those used for similar purposes in edema of the brain and in both cases the procedures seem to be effective within certain limits.

IX. EDEMA DUE TO FAULTY DIET

There appeared during the war in various countries, especially of Central Europe, many cases of extensive edema which were due neither to kidney nor to heart diesase. Sometimes they occurred in an apparently endemic form and were associated with dysentery. At first some authors believed that they were of an infectious nature, but soon it was found that they were caused by a defective, insufficient diet. The dysenteric symptoms were usually secondary, probably due to an accompanying edema of the intestinal mucosa with subsequent ulceration. These patients usually had bradycardia and low blood pressure. Cold weather and work aggravated the condition, while rest in bed often led to a discharge of the edematous fluid and recovery, especially when fat or protein was added to the diet. Addition of yeast, vegetables, or fresh eggs did not have a particularly beneficial effect; there was therefore no indication of a deficiency in vitamins.

Investigators differ as to the factor which is mainly responsible for this condition, whether it is lack of protein, lack of fat, or a deficiency of calories. Perhaps all three factors may play a certain rôle, but probably a deficiency in protein is the most important. It seems that the diet of these patients had not only been lacking in important food constituents, but usually it contained an excess of fluid and salt. The latter substances tend to be retained by a poorly nourished body and thus edema may result.

During the period of edema there is some retention of sodium chloride, but usually the latter is present in the blood only in amounts which are normal, or at most approach the upper limit of the amount found in normal persons; however, there may be a slight increase. When the edema is discharged, the urine becomes very rich in sodium chloride, and at that time the sodium chloride in the blood may be found normal or may have become even subnormal. In the main therefore this salt has been stored in the tissues. A diet poor in sodium chloride may accelerate the discharge of the edema. Administration of sodium bicarbonate leads to a retention of sodium in the form of the chloride and thus may favor the development of edema.

The blood is poor in proteins and lipoids; it is hydremic and often hypoglycemic. The number of erythrocytes may or may not be diminished. There is usually an increase in the non-protein nitrogen, especially in the urea fraction in the blood. The molecular concentration of blood and edema fluid seems to be normal, but the sodium chloride content of the edema fluid has been stated to be greater than that of the blood. It is however possible that we again have merely to deal with an unequal distribution of Cl and Na ions in the blood and edematous fluid respectively, similar to that found by R. Loeb, Atchley and Palmer in other kinds of edema. There may be a slight increase of phosphates in the blood. The edematous fluid is relatively poor in proteins. In the urine an increase in ammonia and a great increase in acetone bodies have been found, a condition which points to the presence of an acidosis.

According to Hülse sodium retention produces edema in these patients in a quantitative manner, 0.6 to 1 gram of this salt causing the retention of about 100 cc. of water. If the edematous fluid is discharged, the sodium chloride is again given off. Sodium carbonate

and bicarbonate and sodium nitrate likewise increase edema, but sodium salicylate and potassium acetate diminish it. Under usual conditions addition of water to the diet of these patients is excreted quantitatively, but if they first receive a diet poor in water, the latter is retained if given subsequently in excess.

At autopsy the kidney, liver, heart, spleen are found to be small; the heart and liver may show brown atrophy. In the intestines there is sometimes ulceration. The lungs may show edema and bronchopneumonia.

Digitalis and theobromin do not usually affect the edema, while thyroid extract seems in some cases to be beneficial; calcium salts also may cause discharge of the edema. The polyuria in some cases accompanying this disease is not influenced by pituitary extract, which is so effective in the polyuria of diabetes insipidus. Rest in bed, addition of protein to the diet and a general increase of the amount of food usually lead to the elimination of the edema.

Related to war edema are several other varieties of edema found in cases of under nutrition.

1. In beri-beri edema may occur, if much water is absorbed. McCarrison found associated with the edema a great increase in the size of the adrenals and a true hypertrophy of the medulla of these glands with an excess production of adrenalin. Notwithstanding these findings this author is not inclined to attribute the edema in this case to the action of adrenalin.

(2) In infants, who are inadequately nourished with a diet in which carbohydrates predominated unduly, or in infants in whom the nourishment suffers as a result of intestinal disease, edema may occur. There may be under those conditions a retention of phosphates and sodium chloride or sodium bicarbonate. Here also the reten ion of sodium chloride may be a factor in the development of edema and, in some cases at least, a diet poor in this salt may lead to the elimination of the edematous fluid. Administration of sodium bicarbonate on the other hand may cause or increase the edema. Acidosis seems to occur in these infants. While in some of these cases lesions have been found in the kidney, in others the signs of kidney disease have been absent. In this connection it is of interest that in infants sodium chloride seems to be eliminated through the kidney less

readily than in older children and thus its administration causes the retention of water, in proportion to the sodium chloride retained.

3. It is possible in animals to call forth edematous conditions through insufficient or faulty feeding. Thus Harden and Zilva produced in a monkey an edema through a long continued diet which, while otherwise satisfactory, was deficient in fat and fat soluble vitamin. In rats edema can be produced through a diet deficient in protein. Addition of casein prevents its occurrence while addition of fat does not have this effect (Denton and Kohman).

Experiments in our laboratory showed that in guinea pigs increased peritoneal transudate is found in cases of underfeeding, without reduction in one particular kind of food stuffs (Hoover). Hoover furthermore found that the same loss in weight produced by a more moderate reduction in diet, but with the addition of thyroid tablets, does not usually lead to an increase in peritoneal fluid. Thyroid feeding prevents therefore the accumulation of fluid in the peritoneal cavity in cases of undernourishment.

4. Joslin, Blum, Falta and others have observed that in diabetes mellitus the addition of large quantities of sodium bicarbonate to the usual diet containing sodium chloride may, in undernourished persons, lead to edema, just as the administration of sodium bicarbonate may, in cases of war edema, in nephritis and in weak infants. In these cases of undernourishment associated with diabetes we have evidently to deal with a condition similar to war edema. In persons undernourished as the result of a deficiency in carbohydrate metabolism sodium chloride and sodium bicarbonate are retained and this leads secondarily to the retention of water. We may assume that in addition the other factors responsible for edema in cases of undernourishment, which we have just discussed, are likewise present in cases of diabetes. It has been maintained that in diabetic patients the edema caused by administration of sodium bicarbonate can be prevented through subsequent ingestion of hydrochloric acid. If this statement should be confirmed, it would indicate that the alkali is responsible for the edema producing effect of sodium bicarbonate in these cases.

5. In old, but normal persons, administration of sodium bicarbonate or sodium chloride may lead to a retention of water and

thus to a gain in weight, while in younger persons these salts are promptly eliminated. In a case of contracted kidney Achard and Ribot found that addition of sodium bicarbonate to the diet led to a partial retention of the sodium ion contained in this salt, and also to a slight retention of the sodium ion of sodium chloride. The sodium chloride content of the blood changed little under this condition and water was not retained under the influence of the bicarbonate. There occurred therefore a dry retention of sodium bicarbonate as well as of sodium chloride in the tissues.

War edema and similar conditions are of great theoretical interest because they are examples of edema without any apparent impairment of the kidney function and without noticeable heart lesions.

As to the interpretation of this edema we may mention the views of Hülse which resemble in certain respects those of M. H. Fischer. Hülse attributes this kind of edema to a weakened heart action, this latter leading to a retention of substances which increase the binding power of water by colloids. He seems to refer such an effect especially to amino acids and he bases this view on his finding that a diet rich in proteins calls forth edema in such patients or at least makes the discharge of the edematous fluid more difficult. This appears contrary to the findings of other investigators who report a favorable effect of the addition of protein. According to Hülse this action of proteins is due to the retention of nitrogenous substances, particularly amino acids; the latter are excreted less perfectly than ammonia. In nephritis, on the other hand, retention of protein does not lead to edema. Hülse locates this edema, as all other edemas, primarily in the cellular organ protoplasm, in contradistinction to the interstitial spaces. We shall discuss the improbability of this latter conclusion in a subsequent chapter. As to the action of amino acids, it is a very improbable assumption that a relatively small retention of these substances could so markedly increase the water binding power of proteins that edema results.

In accordance with Starling's conceptions of lymphformation Epstein explains starvation edema as due to a deficiency in proteins in the blood. Owing to this deficiency the osmotic pressure exerted by the blood is assumed to be lowered and fluid has therefore a tendency to leave the vessels. In a similar way this author explains the edema in nephrosis as due to a diminution in blood protein.

It is most probable that in all these instances we have to deal with an increased transudation of fluid from the blood-vessels which, as the result of undernourishment, have become more permeable to the passage of a fluid rather poor in protein. Water enters the tissues apparently after they have become richer in sodium chloride, as usual the distribution of water following closely upon the distribution of this salt. However, it is possible that not only changes in the vessels and surrounding tissues and in the constitution of the body fluids are responsible for this effect, but in addition the weakened circulation may be a factor that brings about this result. Furthermore the hydremic condition of the blood present in these cases may not only favor changes in the endothelium of vessel wall, but it may also be responsible for a diminished ability of the blood to hold the water within the vessels.

X. EDEMA OF RENAL ORIGIN

A. Edema of nephritis in man

According to Volhard and Fahr we find in parenchymatous nephritis (nephrosis) a diminution in the amount of urine, associated with a retention of water. At the stage preceding the appearance of edema (latent edema, pre-edema), the number of erythrocytes in the blood is according to these authors normal or even increased. There is therefore no dilution of the blood at this stage of the disease; on the contrary, the latter may be somewhat concentrated. In the edematous stage the vessels are assumed to be very permeable; sodium chloride and water enter therefore the tissues and are not available for excretion through the kidney. The elimination of the edematous fluid is preceded by an influx of water and sodium chloride from the tissues into the blood, which thus becomes diluted. This is followed by an increased elimination through the kidney. Under these conditions the percentage of sodium chloride increases in the urine; but inasmuch as the quantity of urine is still small, the absolute amount of this salt excreted remains likewise small. A diet poor in sodium chloride and water favors the discharge of the edema.

These patients lose an enormous amount of protein through the urine, and this causes a hypalbuminosis of the blood, which has

been erroneously interpreted as a true increase in the amount of fluid in the blood. A similar hypalbuminosis occurs in subchronic and chronic nephritis if complicated by nephrosis. The non-protein nitrogen is not increased in this disease. Volhard assumes that under these conditions edema is due to a pathological increase in the permeability of the extrarenal vessels and that this increase in permeability is caused by a toxic substance originating in degenerating kidney epithelium. This kind of edema is therefore mainly the result of extrarenal factors.

Veil, whose studies are of a more recent date, finds the water and sodium chloride concentration of the blood in this disease normal. The main change concerns therefore the communication between tissues and blood, this communication being altered in such a way that water and sodium chloride are drawn from the blood in the direction towards the tissues.

Volhard and Fahr believe that in cases of glomerulonephritis in which edema is prominent, a secondary nephrosis has developed and that the epithelial degeneration of the tubules is the cause of this edema.

No definite relation exists between blood pressure and edema, the tubular change determining, according to Volhard, the edema and the glomerular change the blood pressure.

While in acute glomerulonephritis—which we shall discuss more in detail in the next chapter—most authors find a dilution of the blood, there is, as we stated above, according to Volhard, in diffuse glomerulonephritis, no dilution of the blood, provided it is accompanied by edema. In the glomerulonephritis unaccompanied by edema there may be a dilution of the blood (polyemia). In the latter condition the pathological change concerns principally the kidney and this leads to a retention of water in the blood; in edema, on the contrary, water and sodium chloride are retained in the tissues in consequence of changes in the blood-vessels. In a similar way anuria unaccompanied by edema may be followed by polyemia. In the pre-edematous period on the other hand water is retained in the tissues.

Thus in contradistinction to the views of Widal and other authors, who considered polyemia as a condition leading to edema, Volhard interprets polyemia as a condition which is not usually followed by

edema, but one in which renal insufficiency causes a retention of fluid in the blood. Renal insufficiency furthermore leads often to a retention of non-protein nitrogen, but these substances penetrate into all the tissues and do not therefore cause edema. The views of Volhard have not however been accepted in their entirety by the majority of authors. Thus several investigators failed to find a connection between renal edema and tubular degeneration; furthermore objections were raised by some pathologists to the sharp separation of nephritis proper, an inflammatory condition, and nephrosis, which according to Volhard and others, represents merely a degenerative state of the renal tubules. There may be found not only a hydremic plethora accompanied by retention of sodium chloride in diffuse glomerulonephritis, but according to Reiss edematous patients often have hydremia, while anhydropic patients may show a normal water content of the blood. Veil also finds usually in glomerulonephritis hydremia accompanied by hyperchloremia and the same may even occur in nephrosis (Frey). When the hyperchloremia subsides, a marked excretion of sodium chloride occurs and the hydremic plethora ceases; but hydremic plethora also occurs without hyperchloremia.

More in agreement with the views of Volhard are those of Nonnenbruch, although even according to this author there is no constant relation between renal edema and polyemia (polyemia and hydremia). While in the majority of such cases polyemia is present, if measured by the number of erythrocytes, it is absent in other cases and especially in early cases of edema, particularly nephrotic edema, but also in cases of diffuse glomerulonephritis. On the contrary in this condition the concentration of the blood may be greater than normal.

Nonnenbruch as well as Volhard believes therefore that the origin of the edema in cases of kidney disease may be extrarenal and that it may be caused by changes in the tissues, blood-vessels or in the blood itself. In accordance with this interpretation Nonnenbruch finds that in nephritic patients the drinking of a large amount of water may lead to a greater concentration of the blood even in cases in which the diuresis is inhibited. These observations are interpreted by this author as demonstrating a primary change in the tissues, which draws the fluid from the blood-vessels into the tissues, and this primary tissue change rather than the change in the kidney he

holds responsible for the edema, at least in a certain number of cases. Even in normal persons the drinking of much water may, according to Veil, be followed by an increase in the concentration of the blood, if more fluid is given off through the kidney or into the tissues than is taken in by mouth.

While on the whole these conclusions seem to be justified, we cannot yet quite exclude the possibility that in the condition preceding edema there may have been a very transitory polyemia and hydremia, which stimulated vessels or tissues to such changes that a greater flow of fluid into the tissues followed. This would correspond to the fact that even in normal persons the taking up of much fluid may be followed by a renal secretion which exceeds the intake of fluid and which thus leads to a greater concentration of the blood (Veil). In this case the transitory hydremia or polyemia evidently stimulates the excess kidney excretion. In a similar way in nephritic patients, at the time when they discharge their edema, or when they are ready to do so, an intake of water may lead to an excess elimination of the fluid, although it has been suggested that this reaction is due to a lack of power on the part of the kidneys to concentrate the urine (Haastert).

In chronic glomerulonephritis the excretion of sodium chloride and water can take place in a satisfactory manner and edema may be absent; but at a later stage, if contraction of the kidney progresses, the elimination of this salt occurs with greater difficulty and is always accompanied by a profuse secretion of water. In this chronic stage edema, according to Volhard, is due either to a complication of this disease with tubular degeneration or with cardiac weakness.

According to Veil in cases of anhydropic contracted kidney, movements of sodium chloride take place without the usual accompanying changes in the distribution of water. Thus addition of this salt to the diet does not lead to the usual physiologic plethora, but to the hyperchloremia which is so commonly found in this stage of the disease, even in cases in which a considerable elimination of sodium chloride occurs accompanied by a large amount of fluid.

In a still later stage, when uremic symptoms appear, a hypochloremia occurs which may go hand in hand with a satisfactory diuresis; we may assume that this condition is due to a migration of the sodium

chloride into the tissues and perhaps also into the blood. A similar hypochloremia is also found in cases of poisoning with mercuric chloride and in certain cases of diabetes insipidus, although in the latter condition the mechanism of this hypochloremia may be different. In nephritic hypochloremia the sodium chloride seems to enter the tissue (or blood corpuscles) just as it enters the lungs in the hypochloremia of pneumonia. If in cases of mercuric chloride poisoning the patient recovers, the sodium chloride returns to the blood from the tissues and the blood becomes again normal.

As stated above, in the primary contracted kidney edema is often of cardiac origin. In this condition, in the state preceding the appearance of edema, drinking of much water may be followed by an excessive elimination of fluid. It may be assumed that if this occurs, some occult edema had probably existed previously. If later the heart action becomes sufficiently weak, the elimination of sodium chloride decreases. However, the condition of pre-edema is in these cases usually not so pronounced as in nephrosis. According to Volhard there may be added to the primary contracted kidney a secondary nephritic condition which again may lead to edema. Cystic kidney resembles contracted kidney in that here also polyuria seems to be a frequent symptom. Accordingly in both these conditions edema is usually lacking, although a slight edema may occasionally be observed with cystic kidney.

All the facts mentioned lead to the conclusion that sodium chloride leaves the blood and enters the tissues preceding the appearance of edema, the movement of water following closely upon that of the salt. In accordance with this conclusion are the observations of Leva, who found in patients dying from kidney or heart disease the chlorine contents of the organs to be twice as great, and in the skin even three times as great, as in normal individuals. The water content is not necessarily increased in these cases. But if edema is present, not only the sodium chloride, but also the water content is found markedly increased. There may therefore be a dry retention of sodium chloride and the retention of sodium chloride and that of water do not necessarily take a parallel course in every instance.

If in cases of edema, elimination of the edematous fluid occurs, sodium chloride and water move first from the tissues to the blood

and lead here to a temporary dilution. This is followed by a copious renal excretion of these substances which may cause a temporary inspissation of the blood.

As we stated, it is assumed that plethoric conditions of the blood (polyemia) occur in certain cases. It is believed that in acute glomerulonephritis a hydremic plethora may occur; it is also believed to occur in certain cases of cardiac edema and according to Widal it is found in chronic nephritis preceding or accompanying the edema. Frey observed it in cases of nephrosis. It must, however, be stated that the methods, which have commonly been used in establishing a hydremic plethora, are not above criticism. Thus Widal, assuming that the protein content of the serum is a constant, made use of the refractometric method, and he finds in certain cases a polyemia, when there is reason to believe that there might have existed merely a hypalbuminemia. The determination of the hemoglobin and of the number of erythrocytes in the circulating blood is likewise not quite trustworthy in chronic diseases.

Much more reliable seems to be the method devised by Keith, Rowntree and Geraghty for this purpose. In applying this method, Bock found the blood plasma volume to be normal and constant in cases of chronic nephritis with edema, in cardiac edema and in salt edema in diabetes. The results obtained with different methods thus do not entirely agree and it would be desirable to repeat these determinations, making use of the newer methods.

The factors which cause the tissues or blood-vessels in nephritis to change in such a way that sodium chloride and water are retained in the tissues are not definitely known. The large majority of authors, since Cohnheim and Magnus, assume that toxic substances change the vascular permeability. Volhard, in accordance with a similar hypothesis of Ascoli, suggests that substances which originate in the degenerating tubule cells enter the circulation and thus are responsible for this effect. A certain basis for this view may perhaps be seen in the experiments of Timofiew, who obtained from kidney tissue a lymphagogue substance, which retards the coagulation of the blood and apparently may enter the circulation in animals in which the renal artery or the ureter has been ligated. In such animals an intravenous

injection of sodium chloride solution causes a more extensive edema than in normal animals. Timofiew concludes that such substances constitute an important factor in the development of renal edema; he furthermore assumes that in certain other cases of edema, where renal lesions are absent, similar substances may be given off by other organs. At present these considerations are largely hypothetical. Magnus found that edema follows the intravenous injection of sodium chloride solutions, even in nephrectomized animals, where such substances cannot play any part; so it is doubtful, how far the lymphagogue found by Timofiew is specific for kidney tissue. On the other hand degenerative processes in organs other than the kidney are usually not followed by edema.

M. H. Fischer assumes as the cause of renal edema, as well as of edema generally, the production of acid in the tissues, which would lead to an imbibition of water by the colloids. We shall have occasion to discuss this theory later, and we shall cite facts which make this interpretation very improbable. However, some recent observations of Rohonyi, when taken by themselves, might be assumed to favor Fischer's view. This author found in cases of nephrosis a tendency of the patients to secrete an alkaline urine. According to this author there are indications that this peculiarity is not due to an abnormal excretory activity of the kidney tubules, but to changes in the tissues which lead to an increased movement of Na_2HPO_4 into the blood-vessels, and to an increased retention of the acid phosphates in the tissues. The mechanism of this condition, provided its origin should actually be in the tissues, is at present quite unknown. In a later chapter we shall discuss more fully the possible connection between acidosis and edema.

The edema, or at least the water retention, which may follow the intake of large doses of salicylates and which has been studied by Hanzlik, Scott and Reycraft, may also be due to the injury of the kidney function and may therefore be related to renal edema. The tissues do not seem to be primarily involved and the administration of sodium bicarbonate does not counteract this effect.

There is no indication of a causal relation between blood pressure and nephritic edema. In nephritis we find an increased blood pressure in conditions which tend to be accompanied by a retention of

non-protein nitrogen and in uremia, while in nephrosis (parenchymatous nephritis), in which the edema is very prominent, no marked rise in blood pressure usually occurs. According to Dorner as well as to Miller and Williams, intake of much fluid may cause an increase in blood pressure in chronic nephritis and in arteriosclerotic kidney disease, while in nephrosis Dorner finds that the intake of much water does not lead to a rise in blood pressure. This author interprets this finding as indicating that in those conditions which lead to edema the vessel wall is abnormally permeable and the vessels do not therefore retain the fluid, in contradistinction to the condition found in chronic nephritis, where the blood-vessels do retain it. In acute nephritis the administration of large amounts of water and sodium chloride causes a true plethora and the heart becomes dilated. This may be considered an edema of the blood. A similar dilution of the blood occurs after water intake in cases of onesided nephrectomy.

It is probable that, as the result of renal insufficiency, the movement of water and sodium chloride from blood-vessels to kidney or tissue and from tissue to blood-vessels is interfered with in various ways. Under certain conditions the movement of water and salt in the direction from blood-vessels to interstitial tissue spaces and serous cavities exceeds definitely the movement in the opposite directions. The exact mechanism to which this abnormal movement is due is not known at the present time. However, we may assume that it is initiated by the insufficient secretory activity on the part of the kidney. When it is present in mild intensity it may lend to pre-edema; when it is present in greater intensity it may lead to edema.

A. Edema in acute glomerulonephritis (trench nephritis)

The frequency with which edema was observed in acute glomerulonephritis during the war provided a rare opportunity to study the water and salt exchange under these conditions. The results obtained by different investigators are, however, at least in certain respects, contradictory, especially as to the state of the blood in this disease. Thus Nonnenbruch states that in the early stages, previous to the formation of the edema, or in the beginning of its formation,

the blood is more concentrated, water and sodium chloride leaving the blood at that period to enter the tissues. He interprets this condition as due to an abnormal permeability of the injured vessels. Other investigators, especially Thannhauser, did not observe this concentration of the blood, but on the contrary found that the blood was diluted and that there was an increase in the percentage of sodium chloride. Widal, Benard and Vaucher also found a dilution of the blood and Nonnenbruch likewise observed this condition in the later stages of the disease.

Nonnenbruch concludes furthermore, in opposition to Volhard, that edema may be present in acute nephritis without tubular lesions, the absence of which is shown by the satisfactory excretion of sodium iodide through the kidneys. If a large amount of water is given by mouth to such patients, it causes neither diuresis nor dilution of the blood, but it is retained in the tissues (Siebeck). While the concentration of sodium chloride in the blood serum is somewhat increased, it is normal or subnormal in the urine. As soon as diuresis sets in sharply, the percentage of sodium chloride in the urine increases and the quantity of sodium chloride excreted becomes relatively greater than the quantity of water; but if the discharge of the edema takes a more protracted course, the concentration of the urine remains normal. The condition of the blood in acute glomerulonephritis is similar to that found in the uranium nephritis of rabbits.

If in cases ot acute glomerulonephritis a diet poor in sodium chloride is given, the concentration of this salt in the blood serum does not fall to so low a level as in normal persons. If an excess of sodium chloride is added to the diet, the results vary according to Thannhauser in different cases. The excess may enter the tissues and cause here a rise in concentration of this salt, while in the blood the concentration remains as before. After a few days the sodium chloride concentration of the edematous fluid recedes to its previous level and, if diuresis occurs, the level becomes lower than that of the blood, the salt evidently passing from the tissue into the urine. In other cases the concentration of sodium chloride and the water content of the blood serum increase after the addition of sodium chloride to the diet, while the concentration of this salt in the urine remains subnormal. If the excess of sodium chloride is given in later stages of the

disease, there may still be some slight abnormalities in the distribution of the salt and water. The concentration of sodium chloride in the blood may reach the highest level which occurs in normal persons; at the same time the amount of sodium chloride eliminated through the urine is increased, although the concentration of this salt in the urine is not increased; this is due to the fact that under these circumstances a large quantity of water is secreted by the kidney.

If the excess of sodium chloride is given at the time when a sudden discharge of the edematous fluid occurs, more salt is excreted in the urine than has been added to the diet. Non-protein nitrogen, sugar, uric acid behave similarly to sodium chloride. Thannhauser concludes that insufficiency in renal function is a factor in the development of edema, but that pathological conditions in the capillaries or tissues may also play a part, especially in cases of acute elimination of the edematous fluid, where the mode of elimination resembles that in cases of war edema, in which kidney lesions are absent.

While the diminished excretion of sodium chloride—which exists notwithstanding the high level of this salt in the blood serum—favors the conclusion that the insufficiency of the renal function is at least partly responsible for the edema in this condition, Volhard brings forward some facts which, according to his interpretation, prove that extra-renal factors are primarily the cause of the edema. Thus he finds that in diffuse glomerulonephritis (war nephritis) a diuretic such as euphyllin, causes primarily a movement of water from the tissues to the blood. Similarly a diet restricted as to the amount of water as well as of solid food leads to a movement of fluid from the tissues to the blood. Thus the edema is mobilized preliminary to its elimination through the kidney.

In the state of pre-edema Volhard and Fahr find a retention of water after addition of large quantities of fluid to the diet, and a tendency toward retention of lactose. In this period the tissues take up the water and thus the kidneys do not receive the stimulus that would otherwise lead to the elimination of the edematous fluid. These authors consider the abnormal permeability of the peripheral capillaries as the principal cause of the abnormal movement of fluid and salts towards the tissues. This condition is independent of hydremia and constitutes the pre-edema of Widal. There may under certain con-

ditions exist a hydremia (hydremic plethora, polyemia) which is due to insufficient functioning of the kidney.

According to Volhard the discharge of the edematous fluid is caused by a movement of fluid from the tissues to the blood and kidney rather than by a primary change in the secretory power of the kidney. Various measures may hasten the discharge of the edema; a diet poor in water and salts (Thannhauser), administration of calcium salts or of potassium acetate (Schultz). Purin bodies and intake of much water are usually without effect, as long as the tendency to retention of water exists; but as soon as there is a tendency to eliminate the edematous fluid, pheophyllin or a large amount of water may cause or increase the diuresis (Volhard).

Eppinger in his studies on the effect of thyroid substance on the movement of water and salts found some additional facts which demonstrate the significance of extrarenal factors in the development and discharge of edema. In confirmation of Reichel, he observed that a solution of sodium chloride injected subcutaneously is absorbed much more slowly in cases of nephritis than in normal persons; a solution of this salt given by mouth is eliminated much more promptly than a solution given subcutaneously. Furthermore if blood is withdrawn from the vessels of a nephritic patient the usual flow of water from the tissues to the blood-vessels takes place, but the movement of sodium chloride from the tissues to the vessels is interfered with.

These observations make it necessary to assume that there exists some factor which holds back water and salts in the tissue or prevents their movement from the tissues into the blood-vessels, and that this change is an essential factor in the production of edema in these cases.

M. H. Fischer and M. Hooker assume that in trench nephritis as in all other cases of edema the primary factor is an acidosis in the tissues which leads to a swelling of the parenchyma and intercellular substances. In case such a swelling affects the brain substance, uremia may occur. According to these authors streptococci are responsible for both the kidney lesion and tissue changes. We shall discuss these views in a later chapter.

Summarizing we may then conclude that in acute glomerulonephritis the exchange of fluid and salt at the boundary line of tissue-blood-vessels is altered in such a way that a surplus movement of water and salt takes place in the direction from vessels to tissues. At the same time the movement in the reverse direction is impeded. This condition is primarily caused by the decreased permeability of the kidney tissue and is often accompanied by a damming up of water and salts in the blood-vessels; but it may be present without such a damming up, especially at the period of pre-edema or latent edema. A similar mechanism, leading to altered movement of water and salt at the tissue-blood-vessel boundary, may exist independently of a primary kidney lesion. This mechanism may be influenced by various substances, again without relation to effects of these substances on the kidney activity, and substances or interferences which tend to increase the movement of water and salt at this boundary line in the direction from tissue to blood-vessels may initiate the discharge of the edematous fluid at a time when conditions in the kidney have become more favorable for the increased secretion of sodium chloride and water.

C. Experimental nephritis and edema

Through administration of a variety of toxic substances like arsenic, salts of mercury, cantharidin, chromates and uranium nitrate, an experimental nephritis may be produced in animals. However the number of substances which cause a nephritis associated with edema is much more limited. Thus of all the substances named, uranium nitrate is the only one which regularly causes edema in rabbits, provided this salt is given together with a sufficient amount of water. In a similar manner Dickson produced marked edema in guinea pigs through administration of uranium nitrate, extending over long periods of time.

Arsenic, chromates and even nephrectomy may however, under certain conditions, lead to edema. Thus Magnus observed edema in nephrectomized rabbits or in rabbits to which arsenic had previously been administered, provided an intravenous infusion of a large quantity of a solution of sodium chloride was made. Injection of amylnitrite

may cause edema in chromate rabbits and greatly increases it in uranium rabbits (Richter). In a similar manner the administration of ricin, snake venom, or nephrotoxic serum causes edema in chromate rabbits (Pearce).

It is generally assumed that these substances injure the capillaries and thus cause edema. They are thus supposed to act similarly to the aromatic diamins which are lipolytic and which according to Hess and Mueller after injection produce edema in contradistinction to the aliphatic amins which are non lipolytic and ineffective. It must however be stated that anatomically vascular changes cannot be demonstrated in animals subjected to the influence of these substances except in some cases in the glomeruli of rabbits which have been subjected to uranium nitrate poisoning.

Heineke believed he had demonstrated in the blood serum of rabbits affected with a uranium nephritis a substance which, after intravenous injection into chromate rabbits, caused edema. Subsequent investigations made it however very probable that this interpretation was erroneous and that such a substance did not exist. Schlayer and his collaborators made an effort to prove that all substances causing general edema produce a functional change in the blood-vessels in contradistinction to changes in the tubular epithelium, which latter were thought to be without significance in the causation of edema. However, this distinction between the effect of these substances on vascular endothelium and on tubular epithelium cannot be upheld, and McNider especially has shown that uranium nitrate, which is most efficient in causing edema in rabbits, may leave the renal vessels intact not only anatomically but functionally.

As stated above, of all the substances named, uranium nitrate is the most efficient in causing edema. In order to obtain a clue as to the manner in which this substance may produce this effect, it was of interest to study the way in which the exchange of salts, of sodium chloride in particular, and water between the various constituents of the body, differs in normal, nephrectomized and uranium animals. Richter and Schirokauer first observed a dilution of the blood in the later stages of uranium poisoning. Fleisher and Loeb found an increase in the osmotic pressure of the blood in uranium nitrate rabbits; according to Richter and Roth this effect is due to an increase in

nitrogenous substances in the blood. It is likewise present in nephrectomized rabbits and, according to our findings, in animals subjected to other operations as well, even if the latter are not necessarily followed by edema. Similarly the increase in the concentration of sodium chloride in the blood found in cases of uranium poisoning, is observed also in nephrectomized rabbits. The amount of sodium chloride and other osmotically active substances retained in the blood must be even greater than is indicated by the percentage figures, because of the amount of water which is retained at the same time in the blood. In uranium rabbits, tissues as well as blood contain probably an excess of sodium chloride.

Under these conditions it is of importance that we found certain quantitative differences in the action of these factors; these quantitative differences may have some connection with the production of edema. If we inject intraperitoneally into rabbits, a solution of sodium chloride, a dilution of the blood takes place, which is more marked in the later stages of uranium nitrate poisoning than in the earlier stages; only in the earlier stages it is of an intensity similar to that observed in nephrectomized animals. In the earlier stages following uranium nitrate administration there is furthermore an increased diuresis with a slight relative decrease in the elimination of sodium chloride through the urine; but in later stages there is an almost complete anuria. The osmotic pressure of the peritoneal fluid is a little higher after intraperitoneal injection of a solution of sodium chloride in uranium nitrate rabbits than in normal rabbits; but the osmotic pressure is lower in the peritoneal cavity than in the blood in uranium nitrate poisoning, while in normal rabbits the reverse relation obtains: the osmotic pressure being higher in the peritoneal cavity than in the blood. The most characteristic feature which we observed in uranium nitrate poisoning, is however the diminished absorption of fluid from the peritoneal cavity (Fleisher and Loeb), and this exists notwithstanding the rise in osmotic pressure in the blood in this condition. The decrease in absorptive activity is in sharp contrast to the increase in absorption which is noted in nephrectomized animals (Meltzer and Salant, Fleisher and Loeb) and in animals subjected to non-specific operations (Fleisher and Loeb).

In the same way we found a slightly diminished absorption of sodium chloride from the peritoneal cavity. This decrease in the tendency of substances to pass from the peritoneal cavity to the blood cannot be due to the injurious effect of uranium on diuresis, because it is noticeable already at a time when the secretion of urine is increased rather than diminished by uranium. A regulatory mechanism in the distribution of salt and water, which is present in the normal animal, is evidently disturbed in the nephritic animal. These observations conform to the delayed absorption of salt solution injected subcutaneously in cases of nephritis, to which we have already referred in the preceding chapters.

An increased content in proteins in the peritoneal fluid, which we observed in uranium nitrate animals, is likewise present in nephrectomized rabbits, although in the latter the absorption from the peritoneal cavity is accelerated. However, the diminished absorption of fluid from the peritoneal cavity, as well as in the increase in osmotic pressure of the blood, combined with an increase in the protein content of the peritoneal fluid, is found to a still higher degree in cases of peritonitis. The condition characteristic of uranium nitrate animals resembles therefore the changes observed in cases of peritonitis.

Adrenalin increases absorption of a solution of sodium chloride from the peritoneal cavity in the early stages of uranium poisoning; at that period it has therefore an effect similar to that found in normal animals. But it has only a slight effect in later stages of uranium action. In the later stages adrenalin does not diminish the dilution of the blood—an effect, which it has in normal animals after an intraperitoneal injection—but it still increases very slightly the amount of sodium chloride absorbed from the peritoneal cavity.

While caffeine increases absorption of fluid from the peritoneal cavity in nephrectomized animals, it no longer has this effect in the later stages of uranium nephritis; neither does it produce the lowering in the osmotic pressure of the blood in uranium rabbits, which we observed in normal rabbits.

The changed distribution of sodium chloride in uranium nitrate poisoning suggests that also in this condition this substance may be of significance in the origin of edema, but there are some indications

that the intake of water as such may increase edema in these cases. Thus according to Mohr in uranium rabbits in which the sodium chloride content of the tissues has previously been diminished through a diet poor in this salt, the mere administration of water may cause edema. Richter likewise finds that in uranium rabbits large quantities of water may produce edema; nevertheless it seems that the administration of sodium chloride is in such animals much more effective in increasing edema than the mere giving of water.

We see then that uranium poisoning alters to a very marked degree the movements of fluid from the peritoneal cavity to the blood and to a lesser degree also the movements of sodium chloride; it distinctly retards or even inhibits these movements.

The movement of these substances in the opposite direction, namely, from the blood-vessels to the tissues, or the peritoneal cavity has been studied with contrary results by different investigators. While Schmid and Schlayer found an increased rapidity in elimination of sodium chloride and water from the blood-vessels in the later stages of uranium nitrate poisoning, Boycott and Chisholm, Schwarz and Pollak on the contrary observed a definite retardation in the elimination of various substances (salts, water, lactose and sodium iodide). The experiments of Boycott in particular were repeated by Bogert, Underhill and Mendel with similar results. These latter authors found moreover that a subcutaneous injection of morphine given to dogs or rabbits one hour preceding the testing of the vascular permeability has the same effect on the permeability as the poison used in causing nephritis (uranium nitrate. sodium tartrate). There is therefore in these experiments no indication of an increased permeability of the vessels; and indeed, if the last named investigators attribute the condition of delayed elimination found in uranium nitrate animals to a change in the permeability of the blood-vessels, we could have to deal only with a diminished instead of an increased vascular permeability. We must however consider the fact that in nephritic rabbits the osmotic pressure and the sodium chloride content of the blood are increased and that this factor may not be without significance in the delay in the movement of substances from the blood-vessels to the tissues.

It is one of the problems that remain to be determined in the analysis of edema, how far osmotic changes and how far changes in permeability are responsible for the interference with the movements of water and of dissolved substances in the nephritic organism, and it is possible that osmotic changes may be secondary to changes in the permeability in membranes and that thus in reality both of these factors may be involved.

Boycott and Douglas as well as Lewa found in uranium rabbits an increased retention of water and sodium chloride in the tissues (muscle, skin, kidney) and, as we mentioned above, addition of sodium chloride to the food of rabbits poisoned with uranium nitrate leads to an increase in the edema (Heineke). We may assume that this substance finds its way into the tissues and thus increases edema.

Chisholm was able to extract from the kidney of uranium rabbits a non-coagulable substance which, when injected intravenously, causes a delay in the elimination of substances from the blood-vessels.

Whether the changes which we described are entirely characteristic of uranium nitrate nephritis which is accompanied by edema, and whether they are absent in animals to which substances have been administered which merely produce nephritis but do not usually produce edema, is not yet completely known and needs some further investigation. While according to Chisholm chromate seems to produce the same vascular and tissue changes as uranium, we do not at present know how the exchange of substances between peritoneum and blood-vessels is affected by the action of chromate. However, an observation of Heineke may be of interest in this connection. He noticed that if through administration of chromate a mild nephritis is produced in rabbits, an excess of sodium chloride and water, given by mouth, leads to a retention of the salt and consequently the concentration of sodium chloride rises in the blood and in the tissues, in contradistinction to normal animals, in which under similar conditions an excess of the salt and water in the food is almost completely eliminated. Yet notwithstanding this retention of sodium chloride, edema is usually not observed in the chromate rabbit and the excretion of water takes place effectively following these changes in the composition of blood and tissues, which are thus evidently of a more temporary character than in uranium poisoning. We have presum-

ably to deal with quantitative differences in the action of chromate and uranium, the former substance tending even toward the production of edema, which is however realized only under special conditions. We see then that the effects of uranium nitrate are as follows: (1) An increased dilution of the blood and an increased osmotic pressure and content of sodium chloride of the blood. (2) An increased retention of sodium chloride and water in the tissues. (3) A delayed absorption of water and sodium chloride from the peritoneal cavity. (4) A delayed elimination of water and salts and other substances from the blood. (5) An increased content of colloids in the peritoneal cavity, and (6) a decreased diuresis and, in later stages, changes in the tubules of the kidney which abolish diuresis completely; however, this diminution in diuresis cannot be altogether the direct cause of the first named changes, because the latter may to some extent be present already at a time when the diuresis is still very good. (7) Adrenalin and caffeine have lost their typical accelerating influence on the movement of salt and water in the body in uranium animals. (8) Administration of an excess of water and especially of sodium chloride increases the edema under the same conditions. In contradistinction to uranium, chromate as such does not cause edema, but may lead to edema, if given in combination with certain other substances, especially substances which tend to change the permeability of vessels, while certain substances, which presumably alter the vessels like cyclic amins, may as such produce edema.

Provisionally we may assume that osmotic changes in combination with an increased content in proteins in the peritoneum, and perhaps in the tissue spaces, and alteration of membranes separating the various organs are responsible for this edema; however, further investigations are necessary for a satisfactory analysis of this problem. It is possible that in addition to the factors we mentioned, still another factor is at work in uranium nephritis. Recent experiments of Morawitz suggest such a possibility. This author inserted small plates of agar into the subcutaneous tissue of animals and by weighing determined the amount of fluid taken up by the agar in a given time. Under conditions which tend toward the production of edema, for instance, after administration of uranium nitrate, the agar takes up fluid, while under normal conditions on the contrary it loses somewhat

in weight. Morawitz eliminates changes in hydrogen ion concentration and in osmotic pressure of the surrounding fluid as the causes of this phenomenon. There remains thus the assumption that in uranium rabbits substances are present in the tissue spaces which tend to increase the water binding power of the colloids in the subcutaneous tissue and probably also in the serous cavities. This conclusion agrees with the finding of Fleisher and Loeb who observed that uranium nitrate rabbits show, as far as the behavior of the fluid injected intraperitoneally is concerned, some similarity with animals in which a peritoneal inflammation exists. In both conditions the intraperitoneal fluid is retained; this effect may be connected with the increase in the amount of colloid in the peritoneal cavity which we found in uranium nitrate animals. In addition there may be present a substance of unknown character which increases the water retaining power of these colloids. However, further investigations are necessary for a more complete analysis of the edema in uranium poisoning.

D. The effect of nephrectomy and other operations on the distribution of water and salts in the body and on the formation of edema

In the three preceding chapters we analyzed the factors which lead to the development of edema, if as the result of deficient kidney function the elimination of water and sodium chloride is inhibited. A pathological change in the kidney might affect the distribution of water and salts in the body and in various ways: (1) The insufficient elimination of water and dissolved substances through the kidney as such might give rise to those secondary alterations in the organism which lead to edema; (2) The changes in the kidney tissue might in some way be responsible for those abnormalities in the movement of water and dissolved substances which result in edema, perhaps by leading to the production of a toxic substance which affects the vessel-tissue boundary layer, or (3) a primary factor may cause defects in the kidney as well as affect the distribution of substances in the body and change the mechanisms which determine the movements of substances through membranes. A comparison of the effects of nephritis with those following extirpation of the kidney may perhaps help in deciding among these various possibilities.

Magnus and other investigators found that, while intravenous injection of a solution of sodium chloride isotonic with blood, does not in normal rabbits lead to general edema, but merely to ascites, it may cause general edema in rabbits which have been previously nephrectomized. In these experiments at least a period of several hours elapsed between the nephrectomy and the intravenous infusion of the sodium. In the experiments of Fleisher, Hoyt and Loeb, on the other hand, the infusion followed the operation immediately. In the latter experiments the amount of ascites was increased in nephrectomized animals to a larger extent than could be accounted for by the amount of fluid in normal animals eliminated through the urine; neither could a change in the rate of infusion alter this result. But after nephrectomy the osmotic pressure of the blood is raised (V. Koranyi, Meltzer and Salant, Fleisher and Loeb). Several authors found the blood more diluted and, at the same time, richer in sodium chloride in nephrectomized as compared with normal animals (Schmid and Schlayer, Roger and Garnier, Brandenstein and Chayes). However, in our experiments, in which very large quantities of fluid were injected intravenously, the dilution of the blood was the same in the nephrectomized and non-nephrectomized animals. This difference in the results obtained may, partly at least, depend on the time at which the nephrectomized rabbits were examined.

In agreement with other investigators Fleisher and Loeb found in nephrectomized rabbits the osmotic pressure of the blood serum, as well as its sodium chloride concentration, increased. Like Meltzer and Salant, Achard and Gaillard they furthermore observed an increase in absorption from the peritoneal cavity in nephrectomized animals. We attributed this increased absorption to the increase in osmotic pressure of the blood, which causes the water to move out of the peritoneal cavity into the blood-vessels.

According to Fleisher and Loeb nephrectomy has the following additional effects: It not only increases the absorption of water from the peritoneal cavity, but also that of sodium chloride. Other osmotically active substances pass instead into the peritoneal fluid. As the result of the intraperitoneal injection of an isotonic solution of sodium chloride, the blood becomes therefore more diluted in nephrectomized than in normal animals, while in the peritoneal fluid on the

other hand the protein content is greater than in normal rabbits, as the result of the increased absorption of water. The sodium chloride which is absorbed from the peritoneal cavity in nephrectomized animals is to a great extent passed on to the tissues. As in normal animals, so also in nephrectomized animals, adrenalin causes an increased elimination of sodium chloride and fluid from the blood and the dilution of the blood is therefore decreased under the influence of adrenalin. But, on the other hand, the absorption of peritoneal fluid is not increased by adrenalin in nephrectomized animals, evidently because in such animals adrenalin does not cause the same additional increase in osmotic pressure of the blood which it causes in normal animals. In nephrectomized rabbits caffeine increases the osmotic pressure of the blood and consequently also the absorption of peritoneal fluid, to a marked degree; it likewise increases the absorption of sodium chloride from the peritoneal cavity and the elimination of these substances into the tissues. It also causes an elimination of water from the blood-vessels into the tissues. In nephrectomized animals caffeine accelerates therefore the reversed current of water and sodium chloride from the blood-vessels to tissues, while in normal animals it accelerates the current of these substances from vessels to kidney. Our observations prove thus definite changes in the distribution of water and salt as a result of nephrectomy, and these changes in the movement of water are at least partly secondary to changes in osmotic pressure following nephrectomy.

With these results on the effect of nephrectomy on the distribution of substances in the organism, agree the findings of Nonnenbruch, who observed on the day following nephrectomy a diminution in the number of erythrocytes in the blood as a result of the movement of water and sodium chloride from the tissues into the blood. In addition a certain amount of protein enters the blood according to this author. Thus a true hydremic plethora is produced. The increase in sodium chloride and protein in the blood may amount to as much as one hundred per cent.

As far as these various changes in the movement of salts and water had already been observed by previous investigators, they had been supposed to be specific effects of the lack of the kidney function and of the subsequent retention of substances which normally are elimi-

nated through the kidneys. According to Fleisher and Loeb, however, some of the effects of nephrectomy do not specifically depend on an interference with the function of the kidney, but are due to the effect of the operation as such. This applies for instance to the increase in the osmotic pressure of the blood and to the amount of fluid absorbed from the peritoneal cavity. Indifferent operations on organs other than the kidney have the same effect in this respect as nephrectomy. Caffeine also causes an increased absorption from the peritoneal cavity in animals subjected to a non-specific operation, as it does in animals which have been nephrectomized. The current views as to any specificity in the effects of the elimination of the kidney function on the distribution of water and salt in the organism must therefore be considerably modified as the results of these experiments. Every operation as such—but not the anesthesia accompanying the operation—has a far going influence on the exchange of substances between blood and tissues.

We have apparently in this case to deal with a reaction of general significance. Thus accompanying the tuberculin reaction a dilution of the serum is said to occur and, according to Friedemann and Fraenkel, during serum disease a retention of water and sodium chloride can be found. It seems probable that here likewise an increased absorption of fluid from the peritoneal cavity and a dilution of the blood would occur, but data in this respect are as yet not available.

It still remains to be determined whether the effects following nephrectomy are quantitatively stronger and of longer duration than those following an operation elsewhere. This may perhaps be expected to be the case.

In certain respects comparable to the results of nephrectomy, seems to be the effect which may follow obstruction in the outflow of urine, for instance, in cases of prostatic hypertrophy. It has been stated that edema may develop under such conditions.

In general we may conclude that some of the effects observed in nephritis are found after nephrectomy and even nonspecific operations, and that some of the factors leading to edema are already present under these latter conditions. Yet we do not actually observe edema in nephrectonized animals. It may be that the difference between the effects of nephrectomy and of uranium nephritis is merely of a quan-

titative character, or it may be that in nephritis, toxic substances play a rôle, and that these are lacking after nephrectomy.

However that may be, the experiments mentioned in this chapter are of interest because they so very clearly demonstrate the great significance in osmotic and diffusion potentials in the movements of water through membranes within the organism. Furthermore they demonstrate the fargoing influence of operations in general and of various other interferences, not affecting the kidney, on osmotic changes and on movements of substances in the organism.

XI. THE SIGNIFICANCE OF SALTS IN EDEMA

A. The distribution and movements of water, sodium chloride and non-protein nitrogen in the body

In the preceding chapters we have repeatedly found instances of a relation between the distribution and movements of salts, particularly sodium chloride, and of water, and also a relation between the movements of salts and the development of edema. It might therefore be advantageous for the analysis of edema to review some of the more important factors in the distribution of water and salts as contrasted with non-protein nitrogen in the body. It was the problem of edema which led to a more searching study of the movement and distribution of salts and water in the normal organism. Magnus showed that after an intravenous injection of a hypertonic solution, this salt passes first from the blood into the tissues and subsequently from the tissues back into the blood and into the kidney. Following the injection the tissue gives off water to the blood, but this is not sufficient for the rapid elimination of the injected salt through the kidney and temporarily therefore the salt is stored in the tissues. Engels found that the muscles represent the main depot for water in the normal organism, especially after an intravenous injection of a diluted solution of sodium chloride. Next to muscle, the skin takes up a relatively large amount of water, although much less than muscle. Overton made it probable that a part of the fluid taken up by the muscle is stored in the interstices between the muscle fibers proper. According to A. Mayer and Schaeffer a great constancy exists in the water content of different organs; the content differs however in different species.

The percentage of sodium chloride in kidney, lung and intestines is considerable; the absolute amount of this salt is greater in musculature and skeleton but the main depot for its storage is the skin. If much sodium chloride is taken up, it is stored chiefly in the skin from which it is again given off in larger quantities than from other places in case of sodium chloride deficiency (Wahlgren and Padberg). Those organs whose function it is to eliminate it seem therefore to be the principal depots for this substance, and a connection seems to exist between the secretory function of the organ and its function as a storing place for the substance to be secreted. However, the exact point where this salt is deposited in these organs remains, as far a we know, still to be determined.

It is of interest to compare with the behavior of sodium chloride the distribution of some of the organic nitrogenous constituents of non-protein character.

In contradistinction to inorganic salts, amino acids are carried to all the organs after they have entered the blood from the intestinal canal (D. Van Slyke and Meyer). According to Schoendorff, as well as to Marshall and Davis, urea is distributed approximately equally among all organs and the blood. Recent investigations of Becker on the other hand make it seem probable that the total non-protein nitrogen may be unequally distributed in the body, and the finding of Klein, as to the distribution of non-protein nitrogen in heart and kidney diseases, agrees with the latter conclusions.

Wherever water occurs in the body, there are present at the same time colloids, particularly proteins, and crystalloids, among which salts are prominent. Water enters into relation with both of these substances and the proteins especially have a great importance in binding the water. However the effect of the proteins on the water varies in accordance with the state of these colloidal substances. Here we shall refer only to certain aspects of this question, leaving the discussion of the problems in detail as to the relation between water and colloids to a subsequent chapter.

Woodyatt distinguishes between free water and bound water, the latter being in combination with colloids and crystalloids. Only the free water is available for immediate use, the bound water representing a reserve. According to Woodyatt free and bound water

are in an equilibrium. If through an increase of crystalloids or colloids the bound water increases at the expense of the free water, available for elimination, fever is produced. Important as it would be to determine the availability of water for different functions, and the amounts available in each case, there seem to be some difficulties in the classification of Woodyatt. The water bound electrostatically to colloids and diffusible electrolytes and the water which is merely under the influence of osmotic forces in the solution are not well defined at the present time. The latter would essentially represent the free water. According to Woodyatt it would be especially the water of so-called imbibition which would have to be considered as bound water. Now according to Jacques Loeb, osmotic forces are an important factor even in determining the imbibition of protein gels or micellae.

From a practical point of view, it might be preferable to distinguish between, (*a*) the water in the circulating body fluids (lymph and blood); it is especially the circulating water of the body which is available for excretion (Adolph); (*b*) the water in the loose tissue spaces (*c*) the water in the parenchyma of organs generally, (*d*) the water in the special storage places which serve as reservoirs.

We have seen that the distribution of sodium chloride and of water in the body are not identical, especially as far as the storage places are concerned; yet to a great extent their retention and elimination take place in the same direction and manifest a mutual dependence even in the normal organism. This is shown by a series of recent investigations. On a diet poor in sodium chloride, a healthy person loses weight by giving off an excess in water. On the contrary in undernourished persons water and sodium chloride are not excreted in the same ratio as in normal individuals, but retained. According to Veil, after feeding a diet poor in sodium chloride, an increased concentration of the blood is found at a certain point; this is accompanied by a loss of weight and a negative sodium chloride balance. The sequence of events in this case seems to be as follows: In the first twenty-four hours an excess of sodium chloride is excreted through the kidney and sodium chloride moves from the tissues and perhaps also from blood cells to the blood plasma. Still the sodium chloride percentage of the blood is diminished; notwithstanding this diminu-

tion, more salt passes into the urine than is accounted for by the loss in the blood. It must therefore have come from the tissues or cellular elements of the blood. On the second day the blood loses water and becomes more concentrated, an increase in concentration which is similar to that which may occur in complete starvation. If sodium chloride is now added to the food, both the sodium chloride percentage of the blood and its water content increase again. If an excess of sodium chloride is given with the food, an increase of this salt and of water occurs in the blood on the first day, leading to a temporary serous plethora; on the second day both sodium chloride and water pass from the blood into the tissues and on the third day they return to the urine and are secreted.

According to Thannhauser in healthy persons the retention of sodium chloride and water in the blood, after addition of sodium chloride to the diet, is only very slight and less than could be expected from Veil's statements. The results of Veil agree with those obtained by Haldane and Priestly. According to these investigators the intake of water by mouth does not result in a noticeable dilution of the blood, but following the ingestion of the same quantity of an isotonic salt solution a dilution occurs. The increase in concentration of the blood under the influence of a diet poor in sodium chloride to which we referred above, and the significance of this salt for the retention of water, become still more evident under special conditions when for other reasons a loss of water occurs. Thus in the mountains a diet poor in sodium chloride may cause an increase in the hemoglobin of the blood. Similarly perspiration in a person with a deficit of sodium chloride in the diet leads to a concentration of the blood. The deficit in sodium chloride evidently prevents an efficient movement of water from the muscles and other tissues to the blood. A similar concentration of the blood may follow perspiration under conditions which lead to a rise in temperature. It is different under normal conditions; here, on the contrary, increased perspiration induces movement of water from the muscles to the blood, which may more than compensate for the water lost through the skin and may lead even to a temporary dilution of the blood (Cohnheim, Table, Gross u. Kestner, Cohn, Plant u. Wilbrand). The importance of sodium chloride for the economy of water in the organism is also

evident if water is lost through diuresis. A diet deficient in sodium chloride delays or prevents the body from making good the loss of water caused through caffeine diuresis; and correspondingly caffeine causes a greater diuresis in an organism which has previously been made deficient in sodium chloride (Bogendörfer).

Drinking of water may cause diuresis, if the organism has previously received a sufficient amount of water; but after a preceding diet rich in sodium chloride and relatively poor in water, it does not cause diuresis (Siebeck). The diuresis may lead to the elimination of an amount of water which is greater than the excess of water ingested, which induced the diuresis. The amount of the water and salt, ingested in the period preceding the observation, determines the mode of reaction to a new water intake, not only in normal persons, but also in patients suffering from kidney disease, and in particular does the amount of water administered in the period preceding the test determine the capability to eliminate water given in excess. We must assume that under these conditions salt and water which are stored in the body are not retained in the blood, but in the tissues. Thus Veil found in a young diabetic a retention of sodium chloride in the tissues which was accompanied by a lowered amount of sodium chloride in the blood; in a similar way, water taken in excess, does not necessarily lead to a dilution of blood, but it may be transported to the tissues. This condition, if it becomes quantitatively stronger, gradually passes into latent edema or pre-edema, which precedes the open appearance of an edematous state under pathological conditions. Conversely if, after an excess intake of water, the water is abundantly eliminated through the kidney, a considerable dilution of the blood may be present, owing to the passage of water from the tissues into the blood preliminary to the elimination of the water through the kidney.

We have already mentioned several instances in which a disturbance in the water and sodium chloride equilibrium, at a certain place in the body, leads to an excessive counter move, a reaction which more than balances the disequilibrization caused through the primary disturbance and which may thus lead to a secondary disequilibrization. Only gradually regulating mechanisms set in and correct again this excessive reaction. An additional example of this condition is the

following: When hypertonic glucose solutions are injected into rabbits (Lipschitz) or man (Bürger and Hagemann), the blood becomes at first diluted as a result of the entrance of tissue fluid into the blood. This fluid is relatively poor in nitrogen and salts and the blood is therefore likewise temporarily poorer in salts and nitrogen. The hydremia however induces diuresis and, as a result of the excess elimination of fluid through the kidney, the blood now becomes more concentrated. This change is accompanied or followed by an increased passage of sodium chloride and water from the tissues to the blood. Therefore a second hydremia occurs, which may be associated with a temporary hyperchloremia, and this is gradually corrected through the activity of the kidney.

Under ordinary circumstances the retention of water which follows the retention of sodium chloride, or certain other substances, is merely a temporary condition, which lasts only until the substance taken up in excess has been eliminated; but if the salts cannot be satisfactorily eliminated through the kidney, they may, as Blum, Aubel and Haüsknecht point out, migrate into the serous cavities and thus cause edema. This agrees with the conception that the serous cavities act as reservoirs in which substances are stored which, under normal conditions, would have been eliminated mainly through the kidney.

While therefore changes in sodium chloride and water concentration in the body go usually hand in hand, they, may, as we have mentioned above, in certain cases be independent of each other. Thus in rabbits poisoned by uranium nitrate and given a diet rich in sodium chloride and poor in water, a dry retention of sodium chloride can occur, especially in the skin (Leva). Even in normal individuals, if the water intake is diminished or the loss of water is increased (for instance, under the influence of the desert climate), a dry retention of sodium chloride may likewise occur (Cohn, Bickel).

Conditions prevailing in certain tissues may lead to an abnormal percentage of sodium chloride in the blood. This occurs, for instance, in pneumonia where the blood becomes relatively poor in sodium chloride, because this substance, as well as water and proteins, show a movement towards the lung. If the crisis occurs, sodium chloride returns again to the blood (Von Hoesslin, Snapper, von Monokow). There is reason for assuming that in pneumonia, as in all foci of inflammation,

the concentration of the hydrogen ions is increased and it has been suggested that possibly as a result of this change the proteins in the exudate become converted into kations and therefore begin to bind the chlorine ions. But there is in the pneumonic exudate, according to Blum, Aubel and Hausknecht, not merely a surplus of chlorine, but also an increase of sodium and for this and other reasons such an interpretation is presumably not correct. However, the increase in osmotic pressure present in inflammatory foci may possibly be partly responsible for the movement of water from the blood and lymph to the lung. The retention of chlorides in pneumonia and certain other febrile diseases was attributed by Snapper to a change in the permeability of the tissue for the chlorine ion. He claimed to have actually demonstrated such an increased permeability in the case of the erythrocytes. However, Siebeck showed that the exchange of the chlorine ions between serum and erythrocytes is identical under normal conditions and in disease. A similar movement of sodium chloride and water seems to occur in cardiac edema of the lung. Here also immediately following the beginning of the edema, the salt and water show a decrease in the blood.

Altered conditions in the tissues are an important factor in other instances also in determining the movemen' of sodium chloride and water. Thus Magnus-Alsleben, Nonnenbruch and Gerhardt found that in certain cases of nephritis, or in heart disease, which is associated with passive congestion of the kidney, the kidney excretes promptly a solution of sodium chloride given intravenously, but holds back fluid or salt given per os. It may however be that in such cases the kidney responds only to the stronger change in concentration following intravenous injection, but is unable to respond to the more gradual change in concentration after oral administration. In normal individuals results seem to be different. In this connection it is of interest to recall the observations of Ginsberg and others, according to which in normal dogs water given by mouth causes diuresis, while intravenous or subcutaneous injections of water do not have this effect.

From all of these studies, as well as from those of Siebeck, Öhme and from the experiments of Eppinger and others, which we shall discuss later, it follows that the condition of the tissues is a deciding

factor in determining how much water and sodium chloride shall be excreted through the kidney, and it follows furthermore that the composition of the blood in itself is not sufficient to explain the changes in the economy of water and salt.

The facts which we have recorded in this and in some previous chapters, and to which we shall add in subsequent chapters, suggest that the movements of salt and water in the body are one connected mechanism, a disturbance at one point of this mechanism leading to correlated and compensatory changes elsewhere. The question remains to be answered how this compensatory regulation takes place. The following observation of Priestly suggests that very slight differences in concentration, if they persist during a sufficiently long period of time, may account for considerable movements of water and salts. After an intake of a large quantity of water by mouth, diuresis follows without being preceded by a noticeable dilution of the blood. However, according to Priestly the electric conductivity of the blood is in such cases slightly decreased and the small decrease in the concentration of salts in the blood may be sufficient to set in motion the regulatory activity of the kidney. The resulting polyuria can be prevented through the subcutaneous administration of extract of the posterior lobe of the pituitary gland.

The drinking of excessive amounts of water is harmless as long as the normal channels of excretion function normally. If by some means this process of excretion is interfered with and the stream of surplus water is turned towards the tissues, serious consequences follow. Thus Larson, Weir and Rowntree observed that if dogs are given 3 cc. pituitary extract and soon afterwards an excess of water, symptoms of poisoning, which indicate very strongly an edematous condition in the cranial cavity, ensue. An excess of water may act similarly in certain animals even without pituitary extract. General edema or an increase in the plasma volume of the blood are however not found in such cases, but there may occur an increased blood pressure and increased intracerebral pressure; administration of hypertonic salt solutions is curative in such cases (Larson, Weir and Rowntree).

In man, similar effects have been observed as the result of an excessive drinking of water, in cases in which by some means the prompt

elimination of the water is prevented. Thus in patients with chronic nephritis and hypertension, the administration of large quantities of water may cause not only an increase in blood pressure (Miller and Williams), but also changes indicating increased intracerebral pressure, and apparently pre-edematous conditions (increase in weight, fullness of abdomen) (Rowntree).

In diabetes insipidus an excessive amount of water is taken by mouth without any symptoms of water poisoning becoming noticeable, such as those observed by Rowntree and others. While there may sometimes exist in this disease a hyperchloremia (Veil), an increase in the volume of blood is not observed (Rowntree); a very diluted solution of sodium chloride moves from the tissues to the blood and from the blood to the kidney and the movement continues even after the excessive drinking of water has been interrupted.

According to Erich Meyer and Meyer-Bisch the changes in the movement of water and salt from the blood to the kidney and from the tissues to the blood are coördinated with each other. Pituitrin causes a reversal of this current; under the influence of this substance water moves from the blood to the tissues and Rowntree found accordingly that, after the administration of pituitrin, the giving of water in the large amounts to which the patient had been accustomed results in marked toxicity, and that even a mild anasarca may develop, in consequence of the excess of water being carried to the tissues.

Disregarding the passage of food substances from the capillaries to the tissues, which occurs generally and continuously, we may assume that a correlation exists between the current of water and dissolved substances, from the blood to the kidney and from the tissues to the blood. The latter current may be reversed under certain conditions. Changes at one point call forth corresponding changes in other parts of the system. Mechanisms apparently exist which correlate these two currents in a definite way as to their intensity and direction. The changes induced tend to be excessive at first and only gradually assume their normal character. In this respect, they resemble reactions to stimuli, and to regenerative processes, where at first the response may likewise be excessive. However, not all of the tissues are equivalent in this respect, but certain tissues form more or less specific reservoirs for certain substances.

The mechanism through which these coördinations occur is imperfectly understood at present, but it seems very probable that osmotic and diffusion potentials and perhaps also electrostatic forces leading to endelectrosmosis together with changes in the permeability of certain membranes, play a prominent part in it and that in particular the movement of sodium chloride is one of the important factors which determines the movement of water.

We may then assume that the currents from the blood to the tissues on the one hand, and to the kidney and other places of elimination on the other hand, balance each other, a current in the one direction detracting from the other. Factors that tend to weaken the current towards the kidney strengthen the current towards the tissues and conversely, factors that draw the current to the tissues weaken the current towards the kidney. But these currents tend to keep the blood volume and the blood constitution constant as much as possible, and in addition tend to reëstablish the volume and the constitution of the blood after they have been temporarily disturbed; they have therefore a regulatory character. As we stated salts, especially sodium chloride, play a part in this regulative mechanism. There is reason to assume that the protein content of tissues and of the fluid material in the interstices of the tissues, specific organ activities, the excretory cell activities and the permeability of capillaries play likewise an important rôle in these processes. In addition we have found facts which point to the conclusion that certain substances have a specific influence on these currents and may reverse their direction under certain conditions and this experimental reversal of the current we shall discuss still further in a subsequent chapter.

Added to the main currents just mentioned are supplementary ones which play the part of safety currents; they are directed primarily into the peritoneal and pleural cavities and secondarily into the tissue spaces. These cavities play therefore the part of overflow vessels and they are a last safeguard tending to uphold the constancy of the blood composition.

It follows from these statements that a consideration of the composition of the blood alone is insufficient to account wholly for the elimination of substances through the kidney, inasmuch as the amount of water, sodium chloride and other substances present in certain

tissues, as well as certain specific substances which probably alter primarily the permeability of membranes, determine the direction of the current either towards the tissue or towards the blood and kidney.

B. Sodium chloride in its relation to edema

In the preceding chapter we have discussed the significance of salts, especially of sodium chloride, in the movements of water within the organism. In this chapter we shall deal with the effect which sodium chloride and certain other salts have on the development and intensity of edema and on the elimination of the edematous fluid, and we shall attempt to consider connectedly some of the facts to which we have referred above at various places. We shall thus correlate the function of these salts in the distribution of fluid in the normal individual with the same function in the pathologically changed organism.

The knowledge of the relations between salts and edema was established step by step. Bartels and Grainger Stewart believed renal edema to be due to the insufficient elimination of fluid through the kidney and to the subsequent development of hydremic plethora which led to the transudation of water into the tissue spaces. With the advent of physical chemistry, attention was directed, particularly by Koranyi, to the importance of osmotic changes in the causation of edema. He found in nephritis and pneumonia a significant change in the osmotic pressure; it was increased in the blood and diminished in the urine. But in addition this author, in common with some other investigators, was already aware of the special significance of sodium chloride in edema and he held the opinion that the development of edema depended less on the osmotic pressure, as such, than on the relative increase of sodium chloride in the blood, as compared with that of other osmotically active substances. This ratio between sodium chloride and other osmotically active substances was found increased in various conditions and in particular in cardiac incompetency. Other investigators had likewise observed a retention of sodium chloride in various diseases, among which renal affections were prominent. It is, however, mainly due to the work of Achard, Strauss and Widal that the significance of sodium chloride in the development of edema has been generally recognized. Widal found that in certain cases of nephritis the edema increases pari passu with the amount of

sodium chloride given with the food. Conversely, Strauss and Widal showed that the administration of a diet, which contains a minimum amount of sodium chloride, constitutes an efficient treatment of renal edema. Strauss especially emphasized the conclusion that in edema the retention of sodium chloride is the primary condition and that it is followed by the retention of water. This was also shown to be the case in experimental chronic nephritis (Heineke). Widal observed furthermore that edema is preceded by a condition which he called "pre-edema," in which the retained sodium chloride holds back water without as yet causing a visible collection of fluid in the tissue spaces and serous cavities; merely an increase in weight of the individual indicates this preliminary retention of water.

It must however be stated that these views were not generally accepted. Some investigators were doubtful as to the preponderating influence of sodium chloride in edema (Mohr, Blooker, Vogel), especially in view of the fact that a restriction of this salt in the diet did not, in all cases, have a favorable effect on the edematous condition.

Notwithstanding these objections, there can be no doubt as to the very great importance of the retention and distribution of sodium chloride in edema and this importance is now almost generally recognized. This does not apply only to renal edema; thus, according to L. F. Meyer, the addition of sodium chloride aggravates the water retention in infants suffering from so-called idiopathic edema.

There is, however, still some doubt as to the mode of action and the cause of the retention of this substance. Widal and Strauss held that the retention of sodium chloride was entirely due to the inability of the kidney to eliminate it. Ambard, a collaborator of Widal, determined the relative concentration of this salt in the blood and urine, which regulates its excretion, and he found a threshold concentration for sodium chloride in the blood, below which it is not excreted. This threshold is raised in nephritis; it also varies with the concentration of sodium chloride in the blood.

It may be of interest here to state that for urea, in contradistinction to NaCl, a threshold does not exist, and that while according to Widal the retention of urea and other nitrogenous substances is responsible for uremia, they are of no significance in the development of edema, the latter being caused mainly by the retention of NaCl.

Widal assumed furthermore that NaCl injures the kidney tissue, producing a local renal edema and that the withdrawal of sodium chloride from the food may lead to a restoration of the normal condition of the kidney and thus bring about the elimination of the edematous fluid. Widal, Ambard and Weill also concluded that in nephritis sodium chloride is increased in the body, whether edema is present or not. If owing to the rise in the threshold of the kidney for sodium chloride elimination, sodium chloride is retained in the blood to a greater extent than urea, edema occurs. Similarly Strauss considered changes in the kidney to be the primary cause of the sodium chloride retention.

These views of Widal and Strauss as to the exclusive significance of the kidney in the retention of sodium chloride have now been abandoned by the majority of authors. It is known that the retention of this salt may occur in heart disease, in infectious diseases, especially pneumonia (von Hoeslin), as well as in pernicious anemia and in anemia caused by trypanosomes (Christian, Steinfield). Furthermore Achard showed that there is no correspondence between the concentration of sodium chloride in the blood and the intensity of edema. There may on the one hand be hyperchloremia without edema, and on the other hand there may be a normal sodium chloride concentration in the blood with edema, and there may even be hypochloremia associated with a retention of sodium chloride. There is therefore no relation between the capability of the kidney to eliminate sodium chloride and the actual retention of this substance in the blood and the subsequent edema. Achard held therefore that, in the main, tissue changes are responsible for the retention of this salt, and the experiments of Castaigne, as well as other facts, which we have mentioned, or to which we shall refer in later chapters, seem to prove directly the significance of extrarenal factors in the retention of sodium chloride.

We may then consider it as certain that the retention of sodium chloride in the blood is not directly responsible for edema, but rather the retention of this salt in the tissues. The problem which remains to be solved concerns the factors which cause this retention in the tissue. Is it merely the failure of the kidney to eliminate this salt properly which leads to a storing up in the tissues, or, is this process

of tissue retention due not to the retention of the salt as such, but to changes which take place in the blood-vessels or tissues through the action of certain substances produced by the diseased kidney? Or are both the retention as well as a toxic change in blood-vessels and tissues responsible? We must confess that the exact mechanism which leads to the retention in the tissues is hypothetical; we know it occurs in normal individuals under various circumstances, as well as under certain pathological conditions, prominent among which are kidney lesions. The differences under normal and pathological conditions are mainly of a quantitative character affecting duration and intensity of the change. At present it appears most probable that the insufficient function of the kidneys and the subsequent retention of substances leads to alterations in the exchange of these substances between tissues and blood-vessels. That the kidney plays a part in the retention of sodium chloride would also be in accordance with the conclusions of Schlayer, Hedinger and Takayasu, who showed that uranium nitrate not only makes the renal vessels impermeable to sodium chloride and water, but that in addition this effect appears at an earlier date after administration of uranium nitrate, which causes edema, than in the case of chromate or mercury poisoning, which does not usually lead to edema. This impermeability of renal vessels is believed by these authors to be followed by an increased permeability of the cutaneous vessels, which latter is held to be responsible for the anasarca. However, as we have stated above, such an increased permeability of the cutaneous vessels has not as yet been demonstrated in the case of uranium rabbits and has even been made improbable through the experiments of Boycott and Mendel. The recent studies of Blum, Aubel and Hausknecht, to which we referred above, on the other hand, again confirm the intimate relation between the sodium content of the blood and tissues and the amount of water which is retained in the tissues.

As to the constituent of sodium chloride which is responsible for the effect of this substance on the distribution and movement of water, some of the earlier authors, especially Widal and his collaborators assumed that the edema producing effect is to be attributed to the anion chlorine. However, not only sodium chloride but the administration of some other sodium salts and especially sodium bicarbonate

may likewise cause the development of edema. Widal assumed consequently that the ingestion of sodium bicarbonate is followed by a retention of sodium chloride and that the chloride thus retained is the direct cause of edema in such cases. Accordingly, sodium bicarbonate was found to be less effective as an edema producing agent than sodium chloride and a combination of sodium chloride and sodium bicarbonate was more effective than either alone. Labbe and Guerithault, on the other hand, observed that sodium bicarbonate may cause edema without retention of sodium chloride.

Of special interest in this connection are the observations of Pfeiffer, Magnus-Levy and others, who found that in contrast to sodium chloride the administration of potassium and calcium chloride does not cause a retention of water but that these salts are promptly eliminated through the kidney and may even lead to an increased discharge of sodium chloride and may thus diminish edema. This applies to the movements of water in persons with nephritis as well as in normal persons. Moreover, according to Magnus-Levy potassium acetate may lead to the discharge of edema even in cases where diuretin is without effect. It seems furthermore that sodium bromide can take the place of sodium chloride in causing retention of water (Bogendörfer), and, according to Richter, sodium phosphates likewise act similarly to sodium chloride in producing edema in uranium rabbits. In edema due to malnutrition also other sodium salts can take the place of sodium chloride (Hülse).

In acute infectious diseases potassium ions can be promptly excreted, while sodium ions are retained, and according to Limbeck following the crisis in pneumonia, the excretion of sodium ions is much more marked than that of chlorine ions. We must assume that in the latter case other anions have taken the place of chlorine. On the other hand there is the contrary observation of Moraczewski, who states that in pneumonia the chlorine of potassium chloride is retained as well as the chlorine of sodium chloride.

Of particular interest are recent experiments of Blum, Aubel and Hausknecht. These authors put nephritic patients on a salt poor diet and then added alternately corresponding quantities of potassium chloride and sodium chloride. They found both salts to be retained, the sodium retention to be accompanied by an elimination of po-

tassium, while the retention of potassium led to an excretion of sodium. But only a retention of sodium chloride was accompanied by a gain in weight due to the retention of water. Potassium salt did not have this effect. The retention of water is therefore, they conclude, a specific effect of the sodium ion.

All these facts make it very improbable that the chlorine ion is responsible for the retention of water. It is the kation which has this effect and in particular the sodium. Potassium and calcium act differently. Sodium bicarbonate is less effective than sodium chloride, perhaps because the bicarbonate ion is eliminated more readily than the chlorine ion and thus carries with it some of the sodium ions. We may furthermore, for the same reason, assume that if sodium bicarbonate is administered, chlorine ions are substituted for a certain number of bicarbonate ions. It has thus become very probable that in all these conditions it is mainly the kation sodium and not the anion which causes edema.

Does a relation exist between the retention of non-protein nitrogen and edema? In severe cases of nephritis the non-protein nitrogen is increased in the blood (Ascoli, Strauss); especially the urea is is increased but creatinin and uric acid may also be increased (Folin and Denis, Myers and Fine). While under these conditions the percentage increase of urea is greatest in the blood, the greatest total quantity of this substance is found, as we have already mentioned, in the muscle tissue (Becher). An increased quantity of non-protein nitrogen in the blood is likewise found after nephrectomy —an operation which is supposed to stimulate the breakdown of protein—and it is furthermore observed in cases of wound shock (Duval and Grigaut). The recent studies of Klein make it seem probable that in some cases of nephritic and cardiac edema, non-protein nitrogen may be temporarily stored even in the edematous fluid and from here proceed into the blood and subsequently be eliminated through the kidney at the time of the discharge of the edematous fluid. Notwithstanding this fact as we have stated above, no relation exists, as far as we know, between this retention of nitrogenous substances of a non-protein nature and edema; the distribution of these substances may on the other hand possibly be related to the development of uremia. Widal particularly drew attention

to this antagonism between salts whose retention causes edema, and urea, the retention of which may cause uremia.

It may thus be stated that substances, which penetrate as readily into cells and tissue as does urea, are not apt to produce noticeable changes in osmotic pressure and unequal distribution of water, but that the latter may be caused by certain inorganic salts, which penetrate not at all or only with greater difficulty into cells, and tissue substance proper, and that edema is due to a high intensity of such an unequal distribution.

We may conclude that under normal, as well as pathological conditions, it is mainly—but perhaps not exclusively—the sodium ion which determines, through its movements, the movement of water in the body. We have reason for assuming that the effect of sodium in the development of edema is not different from the effect of this substance on the movement and distribution of water in general; it has the special action of producing edema only when under pathological conditions certain factors act in such a way that the abnormal distribution of sodium is increased in duration and intensity. It exerts this function apparently through the same mechanisms through which it acts on the distribution of water in the normal organism. These factors, which change the current of sodium and influence the intensity of this change, are evidently the essential causes of edema and sodium is a realizing factor. As to the mechanism, through which sodium determines the distribution of water, it is probable that it acts mainly through its influence on osmotic pressure in the tissue spaces primarily and in the blood and organs secondarily. How far in addition electro-endosmotic factors come into play in this effect, we do not know at the present time.

It is of interest to consider the reason why this specific action should attach to the sodium ion. It may be due to the fact that sodium is the most common and relatively the most indifferent ion in the body fluids, and that it is normally present in the body fluids in much larger quantity than all the other kations. Associated with this fact is the relative lack of specific effects of this substance. Potassium and calcium, because they are normally present in so much smaller quantities, set in motion mechanisms which lead to their elimination from the body fluids as soon as their quantity becomes abnormal, and thus

they may cause, among other effects, diuresis. Specific organs of excretion are stimulated much less by sodium and so it can produce osmotic effects within the body. We may also have to consider the fact that in all probability the proteins are present in the body fluids largely as sodium proteinates and that this may in part account for the tendency of sodium to be retained under pathological conditions.

XII. THE INFLUENCE OF CAFFEINE AND RELATED SUBSTANCES ON THE MOVEMENTS OF WATER AND SALTS IN THE NORMAL AND NEPHRITIC ORGANISM

The diuretics of the Purine group have in certain cases of edema a noticeable accelerating influence on the discharge of the edematous fluid. It was therefore of interest to determine in what manner these substances affect the movement of water and salts, especially of sodium chloride, in the body. Weber injected salt solutions subcutaneously and intravenously and found, under the influence of caffeine, a more rapid movement of the solution from the subcutaneous tissue into the blood in the first case and out of the blood into the tissue in the second case. Georgopoulos observed an increased absorption of serum injected into the peritoneal cavity under the influence of caffeine; he attributes this effect to a stimulating action of caffeine upon the lining membrane. Fleisher and Loeb undertook the first systematic study of the effects of caffeine on the movements of salt and water under various conditions which are comparable to those which prevail in edema. We analysed the influence of caffeine on the absorption of an intraperitoneally injected solution of 0.85 per cent sodium chloride in normal rabbits, in rabbits which had been previously nephrectomized or in which another operation had been performed, and lastly in rabbits to which uranium nitrate had been administered one or three days previously. The results are as follows: In the series of normal rabbits caffeine increases the secretion of urine through the kidney and raises very considerably the percentage of urinary sodium chloride. At the same time it lowers the sodium chloride content of the blood serum as well as its osmotic pressure. It exerts this effect on the osmotic pressure of the blood serum even in rabbits which have not been previously injected intraperitoneally with a solution of sodium chloride. Caffeine has therefore a specific

effect on the sodium chloride elimination through the kidney. In consequence of this movement of sodium chloride from the blood into the urine, the sodium chloride contained in an intraperitoneally injected solution of this salt moves more actively from the peritoneal cavity into the blood. Caffeine increases therefore the absorption of sodium chloride from the peritoneal cavity, but on the other hand it does not increase the absorption of peritoneal fluid in normal animals, because it lowers the osmotic pressure of the blood. In such animals following an intraperitoneal injection of sodium chloride a dilution of the blood takes place as a result of the absorption of the sodium chloride solution from the peritoneal cavity. Caffeine diminishes this dilution by increasing the amount of fluid eliminated from the blood-vessels through the kidney.

As we have stated above, every operation of sufficient importance, of whatever kind, raises the osmotic pressure of the blood. In animals, which have been operated upon, caffeine is less effective as a diuretic, although it still produces diuresis and it also diminishes the dilution of the blood by increasing the elimination of fluid from the blood-vessels. Under these conditions it not only causes an increased absorption of sodium chloride but even of fluid from the peritoneal cavity, owing to the rise in the osmotic pressure of the blood.

In nephrectomized rabbits the osmotic pressure of the blood is likewise higher than normal and caffeine causes, in these animals, an additional rise in the osmotic pressure. In consequence of this effect it calls forth an increased absorption not only of sodium chloride but also of fluid from the peritoneal cavity; neither the water nor the salt, however, is retained in the blood, but under the influence of caffeine both are transported into the tissues. Caffeine causes therefore an increased elimination of fluid and sodium chloride into the urine, if the kidney functions; if it does not function, it causes an increased elimination of fluid and sodium chloride from the blood into the tissues.

This effect of caffeine applies in a specific manner so far only to sodium chloride. Other osmotically active substances move in the opposite direction, namely, from the tissues to the blood and into the peritoneal cavity. From these experiments we concluded that the action of caffeine in increasing the elimination of sodium chloride

from the blood or peritoneal cavity is not necessarily due to a specific effect of this substance on the kidney; on the contrary the influence of caffeine upon the composition of the blood may in part, at least, account for the caffeine diuresis. As we pointed out at the time of our experiments, the primary change caused by caffeine may consist in calling forth some condition that causes the sodium chloride and water to leave the blood in the direction towards the kidney, if possible, and otherwise in the direction towards the tissues. There are evidently other tissues which attract sodium chloride and water in a manner similar to the attraction exerted by the kidney. According to Erich Meyer and R. Meyer-Bisch the effect of pituitrin is to some extent analogous to that of caffeine. In diabetes insipidus pituitrin causes a movement of water from the blood and lymph to the kidney on the one hand, and to other tissues on the other hand. The experiments of Rowntree and his associates, to which we referred above, also suggest this conclusion.

While caffeine causes thus an increased absorption of fluid from the peritoneal cavity in nephrectomized rabbits, it does not have this effect in animals which three days previously have received a toxic dose of uranium nitrate, although in this condition, too, the osmotic pressure of the blood is raised considerably. As the result of the uranium poisoning, the increase in absorption is lacking notwithstanding the fact that caffeine causes a slight additional rise in osmotic pressure in the blood; secondary factors counteract in this case the consequences which would otherwise follow upon such a rise in osmotic pressure. Still caffeine effects even in such uranium animals, in which no longer any secretion of urine occurs, a slight movement of water from the blood to the tissues.

Quite recently Nonnenbruch observed that under certain conditions theophyllin causes, in addition to an increased movement of fluid and salt, also an increased movement of protein from the tissues into the blood.

If we compare the effects of caffeine with those of adrenalin, we find that both increase the absorption of fluid from the peritoneal cavity, in those cases in which they raise the osmotic pressure of the blood. Adrenalin increases therefore the absorption of water more generally, while caffeine has this effect only under special conditions. Caffeine

increases the diuresis while it does not increase the absorption of fluid from the peritoneal cavity in normal animals; adrenalin on the other hand increases in normal rabbits both the diuresis and the absorption of fluid from the peritoneal cavity. Both these substances cause an elimination of fluid from the blood-vessels. The most marked difference between caffeine and adrenalin concerns their effect on sodium chloride. While caffeine has a specific effect on the elimination of this salt, adrenalin on the contrary increases the absorption of water more than that of sodium chloride. It does not specifically cause the elimination of this salt from the blood-vessels, and therefore diminishes, rather than increases, the quantity of sodium chloride absorbed from the peritoneal cavity with a unit of water. Conversely it does not cause the opposite movement of other osmotically active substances into the blood and peritoneal cavity, as does caffeine. Caffeine eliminates sodium chloride both through the kidney and into the tissues, while adrenalin is inert in both respects. Adrenalin accelerates the movement of water, but only to a slight extent or not at all that of sodium chloride.

The more recent experiments of Veil and Spiro agree well with and are essentially confirmatory of the results obtained by Fleisher and Loeb. Veil and Spiro administered to rabbits a solution of sodium chloride by mouth and obtained a dilution of the blood in nephrectomized animals. In such nephrectomized rabbits administration of theocin caused a movement of water and sodium chloride from the blood to the tissues; from here these substances are presumably eliminated through the action of certain glands.

The kidney and other tissues are thus coördinated. If under the action of theocin the blood has lost much sodium chloride, it is retained in the blood in a period subsequent to the theocin administration, and now the urine on the contrary becomes poor in sodium chloride. If much sodium chloride has previously been stored in the body, as for instance, in cases of cardiac edema, the diuresis and elimination of sodium chloride under the influence of theocin may continue for a longer period of time than in a normal individual, where the tissues become more readily exhausted.

We see then that in the normal organism caffeine causes a coördinated movement of sodium chloride and water from the blood to

the kidney and from the tissues to the blood. Protein also passes from the tissues into the blood. The elimination through the kidney seems under these conditions to be more active than the movement from the tissues to the blood, and the elimination of sodium chloride through the kidney is apparently, under the influence of caffeine, a primary effect in contradistinction to the effect produced by adrenalin on the movement of this substance and of water. If the passage of salt and water from the blood to the kidney is prevented, the movement occurs in the opposite direction, namely from the blood to the tissues. The movement of water and sodium chloride from the peritoneal cavity to the blood is apparently not entirely coördinated with the movement of these substances from the tissues to the blood, but it is a subsidiary movement and to some extent independent of the latter. As we have seen uranium nitrate alters these movements of water and salts completely.

XIII. COLLOIDS AND THEIR SIGNIFICANCE IN THE DISTRIBUTION OF WATER IN THE ORGANISM UNDER NORMAL AND PATHOLOGICAL CONDITIONS

There exist numerous observations in the literature concerning the effect of colloids on the movements of water in the body as well as in vitro. By a simple method Oker-Blum demonstrated this influence in vitro; he showed that the addition of blood serum to the fluid surrounding plates of gelatine prevents water from entering the latter and that the proteins of the serum are responsible for this effect.

From theoretical considerations Starling attributed to the colloids of the blood great significance in making possible the return of fluid from the tissues to the blood-vessels. This author assumed that the greater the difference between the amount of proteins in the blood-vessels, and in the tissue spaces surrounding the latter, the more marked is the movement of water towards the place of greater concentration of proteins. Overton showed that if a colloid is added to the solution in which a piece of muscle is immersed in vitro, fluid may be withdrawn from the muscle. The colloid material in this case attracts water much more strongly than could be foreseen from its

relatively low osmotic pressure. Wessely found that, after an injection of hypertonic salt solutions under the conjunctiva, protein becomes mixed with the injected fluid. He attributes to this fact the slow absorption of an injected salt solution even after it has become isotonic with the body fluid. Similar observations were made by Eppinger after subcutaneous injections of a solution of sodium chloride. This author furthermore showed that the addition of gelatin to a sodium chloride solution causes a great delay in the absorption of the latter. Various investigators established the influence of colloids on the secretion of urine; we shall, however, refer here only to the observation of Ch. Richet who noticed a diminution in the urine after the intravenous injection of a solution of gum. This agrees with the finding of Roger and Garnier and others, that intravenous injections of gum or gelatin cause an increase in the retention of fluid in the blood. The plethora and increase in viscosity of the blood resulting from such an injection may lead to a dilatation of the right heart and to pulmonary edema. In an analogous manner a reduced size of the heart, brought about through hemorrhage or withdrawal of blood, can be restored through an intravenous injection of gum acacia and sugar solution. Ringer's solution on the other hand does not have such a restorative effect (E. Meyer and R. Seyderhelm). M. H. Fischer likewise showed the power of colloids to retain water after intravenous as well as intraperitoneal injection. Boycott and subsequently Bogert, Underhill and Mendel, observed that colloids tend to retard the velocity with which solutions leave the vessels after intravenous injection.

Some recent observations indicate that proteins together with tissue fluid, may spontaneously enter the blood-vessels. If an intravenous injection of 40 cc. of Ringer solution is made with the addition of 6 per cent gum or 5 per cent gelatin, a primary plethora is induced, but the number of erythrocytes again becomes normal at the end of two hours (Nonnenbruch); only if a hypertonic gum solution, similar to that used by Erlanger and Gasser, has been used does a plethora of longer duration ensue. The injected colloids soon enter the tissue and here they may apparently exert an inhibiting effect on diuresis. Within the first two hours the intravenous injection of gum solution calls forth a decrease in the erythrocyte count, owing to the entrance

of fluid into the blood-vessels. According to Nonnenbruch this fluid contains protein; therefore the diminution in the number of erythrocytes in the first two hours is found to be much greater than the loss in serum protein. His calculations indicate that fluid containing about thirty percent of protein enters the blood stream. This stage is followed by a loss of protein (hypalbuminosis) which still persists after the return of the blood corpuscle count to its normal figure. Intravenous injection of a solution free from protein likewise causes the entering of protein into the blood. This again is followed by an excess loss of protein from the blood, after the injected fluid has been eliminated. Similarly after a loss of water through perspiration proteins may enter the vessels together with the tissue fluid (Gron and Kestner, Cohn, Bogendörfer). We have already referred above to the action of colloids in shock (Hogan, Bayliss, Erlanger and Gasser).

The significance of colloids in edema is suggested by the fact that edematous fluids contain proteins and that, in certain cases, factors, which increase or call forth edema, increase at the same time the protein content of serous cavities or tissue spaces. The protein content of the edematous fluid is especially great in inflammatory edema, as for instance, in pneumonic exudate. In rabbits with peritonitis, Fleisher and Loeb found that the absorption of salt solution injected intraperitoneally did not take place, notwithstanding the high osmotic pressure of the blood in these animals. On the contrary, substances which tended to increase the osmotic pressure of the peritoneal fluid were attracted into the peritoneal cavity. Even in nephrectomized rabbits and in rabbits treated with uranium nitrate the peritoneal fluid contained a larger amount of protein than in normal animals. There is a possibility that this increased protein content is at least partly responsible for the diminished absorption of fluid from the peritoneal cavity following the administration of uranium nitrate. In accordance with these findings various authors and especially M. H. Fischer and Eppinger, have attributed great importance to the presence of colloids in the development of edema, as we shall discuss more fully in subsequent chapters.

As might be expected the fluid withdrawn in anasarca contains protein. The quantity of protein varies however in different cases. Beckmann made comparative studies of the protein content of various

edematous fluids withdrawn from the subcutaneous tissue. In glomerulo-nephritis the fluid was richest in protein; it was less so in cardiac edema and in other edema due to mechanically produced congestion; although in these cases the protein content was still relatively marked. The protein content reached its lowest level in war edema and in edema following nephrosis and amyloid kidney. It is of interest that the sodium chloride content of the edematous fluid did not run parallel to the concentration in protein, and further that no relation existed apparently between the amount of edematous fluid retained in the patient and the concentration of the fluid in protein. With these findings agree the recent studies of Haas. According to this author the protein content is highest in acute glomerulonephritis. In kidney lesions of a degenerative character (nephrosis) and in cardiac edema he finds a low or medium concentration of protein. R. F. Loeb, Atchley and Palmer likewise noted a low concentration of protein in ascitic fluid in cirrhosis of the liver and in renal edema—presumably cases of nephrosis or non-acute nephritis—while in cardiac and cardiorenal disease the protein content was higher. In general Haas does not find a parallelism between the severity of the edema and the protein content of the edematous fluid. Only in the pure forms of cardiac edema does such a parallelism exist. We may assume that in the latter condition the amount of edematous fluid and the concentration of protein in the fluid depend upon the retardation in the capillary circulation and upon the increase in permeability of the capillaries, and that this increase in permeability is to a certain extent proportional to the circulatory disturbance. As a rule the great variability of protein concentration depends presumably upon corresponding variations in the permeability of the blood capillaries. Haas confirms the conclusion, to which we referred above, that an increased amount of protein in the edematous fluid is not noticeably associated with an increased amount of sodium chloride. Likewise a high protein content does not prevent a rapid discharge of the edematous fluid. Whenever in cardiac edema the circulation is restored, the elimination of the edematous fluid occurs independently of the amount of protein present in the fluid. Similarly in edema accompanying glomerulonephritis, in which the fluid contains much protein and in which the blood pressure is high, a rapid discharge

may take place concomitant with the fall of the blood pressure; while a slight edema with a low protein content may persist a long time, provided the kidney lesion persists. The protein does not prevent absorption of the edematous fluid.

More recently Gayda and subsequently Ellinger studied the conditions which lead to the production of edema by perfusing blood-vessels of frogs in the Laewen-Trendelenburg or similar preparations with various kinds of fluids. These authors confirm to a certain extent the significance of colloids in edema. They find that the hypertonic solutions of salts or anelectrolytes either prevent edema or they may withdraw fluid from the edematous and even from the normal tissues. Pure serum also was found particularly effective in this respect. Gayda assumes the presence in the serum of two active substances, one coagulable through heat, the other not coagulable; to the latter we have referred in an earlier chapter, in our discussion of the factors which influence the contraction and permeability of capillaries. Correspondingly injection of serum into the muscle tissue of the perfused frog causes here a localized edema and serum injected subcutaneously attracts fluid from the blood-vessels, if the latter are perfused with Ringer solution (Ellinger and Heymann).

The edema in nephrosis is attributed by Epstein to a diminution in the protein content of the blood which results from the loss of this substance through the kidney. In accordance with the conception of Starling he assumes that in consequence of this diminution in protein content the osmotic attraction of the blood for water decreases and that the water, which would otherwise have passed into the blood, is retained in the interstices of the tissues.

As we shall discuss later, through combination with acids or bases, the water binding power of the proteins is increased. Ellinger and Heymann could accordingly show that serum which had been dialyzed against an acid or alkaline solution attracted water, in perfusion experiments, with much greater intensity than did ordinary serum.

Of great interest is also the observation of these authors that perfusion of the eviscerated frog with distilled water leads to an imbibition of the muscle tissue proper, while perfusion with isotonic salt solutions is followed merely by a collection of the fluid in the tissue spaces. It is possible to withdraw again edematous fluid from the tissue spaces

through perfusing the vessels with hypertonic salt solutions or even more actively with hypertonic solutions of cane sugar; still more effective was a perfusion with a 2 per cent solution of gum made up with Ringer's solution. Now, the edematous fluid, as it occurs spontaneously, represents an isotonic salt solution and not distilled water. We may therefore conclude that the edematous fluid will collect in the tissue spaces rather than in the parenchyma of organs proper.

Ellinger and Heymann assume that the osmotic pressure exerted by the protein solutions plays a minor part in attracting water and that it is rather the imbibition pressure of either protein sols or gels on which depends their water binding power. The total water binding power of protein solutions is much greater than could be foretold from an estimation of their osmotic pressure. According to these authors the following factors determine the development of edema in the tissues: (1) the amount of protein present, (2) the combination of protein with acid, and (3) the effect of hormones like thyroid extract which, according to their opinion, exerts an influence on the water binding power of the proteins.

We see that there is reason for attributing a certain influence to the colloids, especially proteins, in determining the development and intensity of edema, although it is as yet doubtful whether this influence is as great as some authors assume. However that may be, it will be necessary for us to inquire somewhat more in detail into the factors that determine the water attracting power of proteins.

In the interpretation of edema the relation of salts to the water binding power of proteins is of special importance. Hofmeister was the first author who investigated this relationship. He found that certain salts diminish, while others increase, the swelling of solid proteins and he arranged anions and also kations in a definite order according to their influence on the water attracting power of protein. A somewhat similar order of ions was subsequently found in various other processes affecting the functions of cells and tissues. Subsequently Spiro showed that acids increase the swelling of proteins and in varied experiments M. H. Fischer determined the antagonistic effect which salts exert on the swelling of the proteins under the influence of acids or alkalies. In accordance with the Hofmeister series, Fischer found a great difference in the effectiveness of various

salts in preventing the swelling of proteins under these conditions, and he recommended therefore certain salts as particularly valuable in the treatment of edema. A. D. Hirschfelder showed however that the differences found by Fischer in the action of various ions are not direct effects of these ions, but depend on the hydrogen ion concentration under which their action takes place. If the hydrogen ion concentration is kept constant, different neutral salts are identical in their action with the exception of sulphates, which depress the water binding power of proteins more than other salts.

The great significance of the hydrogen ion concentration in protein solutions, as a factor in their water binding power, has recently been analysed in a series of investigations by Jacques Loeb and here, furthermore, a beginning has been made in the separation of the various factors which might participate in causing the affinity of proteins for water, which has so far largely been attributed to adsorption. Thus it will be seen that in all probability forces of different character coöperate in bringing about what is usually called the imbibition pressure of proteins.

Three characteristics of proteins are of importance in this analysis. In the first place proteins are amphoteric; they combine with the anion as well as with the kation to form salts, in which the protein molecule furnishes the complementary ion. The hydrogen ion concentration of the solution determines which kind of salt shall be formed. In an acid solution in which the hydrogen ion concentration surpasses that concentration which is characteristic of the isoelectric point of that particular protein, the protein furnishes the kation and the acid the anion. With hydrochloric acid, for instance, protein forms a protein chloride. In an alkaline solution the opposite protein salt forms, namely, a proteinate in which the base provides the kation and the protein the anion. At the intermediate point, the so-called isoelectric point, in which the solution is neither acid nor alkaline as far as the protein is concerned, the protein combines neither with the anion nor with the kation. It does not form salts but exists as a non-iogenic molecule. These conceptions are based on the investigations especially of Michaelis, Sorensen and Jacques Loeb. The latter particularly completed the proof of their general applicability and we shall follow his presentation of the subject. At the isoelectric point

the protein has the minimum of water binding power; the more the acid or alkali that is added to this solution, the greater becomes the water attracting power up to a certain maximum, when a further addition of acid and alkali diminishes it again. Such a relation between ionization of the protein and its water attracting power had already been indicated by Laqueur and Sackur, but the correct interpretation was first given by Jacques Loeb who showed that it is due to the Donnan membrane equilibrium, which develops when a membrane separates a set of ions, one of which cannot diffuse through the membrane, while the other ions can do so. This represents the second characteristic of proteins which they have in common with all substances whose molecule is very large. Thus water is attracted from the outside of the membrane and the more so the greater the amount of acid or alkali which has been added to the protein solution up to a certain maximum, when further addition again depresses the water attracting power. Protein solutions therefore surrounded by a membrane exert osmotic pressure. This osmotic pressure is however only in a relatively small degree due to the protein ions themselves; it is mainly caused by the diffusible ions, which, according to the Donnan equilibrium, are present in a surplus inside of the membrane.

As R. S. Lillie has shown, salts added to the protein solution depress its osmotic pressure. According to Jacques Loeb this is again due to the effect of the salts on the Donnan equilibrium, which latter causes a diminution in the excess of diffusible ions within the membrane. We have therefore in this case to deal with an indirect action of the salts.

But proteins have still a third property, in common with other colloids, namely, that of forming larger aggregates of ions or molecules, micellae, emulsified or suspended particles; the latter have a special water binding activity, which, as Jacques Loeb, in accordance with the findings of Procter and Wilson, has shown, is also regulated by the Donnan equilibrium. It is due to the fact that the protein molecules or ions in the micella, in contradistinction to the diffusible ions, cannot move freely. In this case the Donnan equilibrium is influenced by the same factors which affect the osmotic pressure; in particular, it is depressed by the addition of salts and with this depression in the osmotic pressure goes hand in hand a depression of the water attracting power of the colloid solution. Exceedingly large

amounts of water are thus included in such micellae and the greater the number of micellae and the more water the latter include, the greater becomes the viscosity of these protein solutions. This viscosity is determined therefore by the Donnan equilibrium. If the protein micellae become very large a gelatinization of the solution may take place. In this case the water binding power of the gel is again determined by the equilibrium.

Wherever a Donnan equilibrium is present, a potential difference develops either between the solution of a colloid inside and the fluid on the outside of the membrane, or between the gel or micellae and the surrounding fluid. The size of this difference in potential is again quantitatively determined by the Donnan equilibrium and it is altered by the addition of salts in the same direction as the equilibrium. It is always the ion with a charge opposite to that of the protein ion in the protein salt which has the depressing effect, just as, according to Hardy, the opposite ion has the power of precipitating colloids in suspension. In both cases the effect of this oppositely charged ion increases rapidly with increasing valency.

In case water moves through the pores of a membrane of protein character, potential differences may originate between the water and the membrane, which according to Jacques Loeb are again due to a Donnan equilibrium, developing between the non-movable constituent of the membrane and the diffusible ions. Under these conditions the water assumes a charge which is opposite to that of the protein ion. The electric charge of the water may influence the direction and rapidity of movement of water through the pores of the membrane. Thus if in the solution within a membrane, ions with a certain charge predominate, the solution may either attract or repel the water; ions with a charge opposite to that of water attract the latter, while ions with the same charge repel it. This becomes apparent however only when low concentrations of the salts are used, otherwise the purely osmotic effects obscure these electrostatic influences.

In addition to these factors which are largely determined by the Donnan membrane equilibrium, molecules or ions of protein may attract water by other means, which are probably chemical in character and similar to those which determine the solution of electrolytes in the solvent. These forces and perhaps other factors of a different

kind may come into play even in case the protein is at or near the isoelectric point. Thus isoelectric gelatin in the gel state may take up considerable amounts of water.

The last named category of interactions between the water and proteins, in which the Donnan equilibrium does not play any part, are mainly responsible for the state of solution or precipitation of the latter substances. Especially bivalent anions like SO_4 may have a precipitating effect on the protein, irrespective of the charge of the protein ion. This precipitating effect is greatest near the isoelectric point where the tendency to form aggregates of molecules is usually great. However, in the case of different proteins the different ions may have specific effects, as far as their influence on solution and precipitation of the protein is concerned; and under certain conditions bivalent kations may increase the solubility of some proteins.

We may summarize, in accordance with the conclusions of Jacques Loeb, the factors which come into play in the interaction between proteins and water as follows: (*a*) There is a peculiar distribution of the diffusible ions which cause the movement of molecules of water into a solution of proteins, separated from the outside solution through a membrane. The blood-vessel wall, as well as probably the membranes surrounding all organized structures in living organisms, have to be considered in this connection. But in the living organism complicating factors which influence the movement of water and dissolved substances frequently come into play. In this connection we may recall for instance the fact to which we referred in a previous chapter that membranes, separating the peritoneal and pleural cavities from the surrounding tissues, follow laws which are different from those holding good in the case of the intestinal wall. (*b*) Whenever aggregates of ionized proteins are formed, differences in the distribution of diffusible electrolytes outside and inside the micellae call forth a higher osmotic pressure inside the micellae than outside. Thus great amounts of water become occluded in the interior of the micellae. It is of importance in this connection that different proteins differ much in their tendency to form micellae. We may assume that the tendency to form such aggregates is much greater in the fibrinogen than in the serum albumin fraction. This source of water attraction acts within the solution; a separating membrane not being required

for this purpose. (*c*) The factors, which determine, in general, processes of solution, apply also to isolated protein molecules and ions. These forces are apparently related to those on which depends chemical affinity. Isolated protein molecules near the isoelectric point, as well as protein ions and also aggregates of isoelectric protein molecules may bind water by these means, and we must assume that each molecule of protein may bind multiple molecules of water. (*d*) It is possible besides that physical forces of capillarity may draw water into large micellae of protein. Protein solutions differ in their water attracting power from solutions of readily diffusible substances through the factors mentioned under *a*, *b*, and *d;* and these combined represent what is often called imbibition pressure. If in addition to the action of the imbibition pressure one molecule of protein may by means of its chemical affinities bind more than one molecule of water, it is clear that the water attracting power of proteins is much greater than could be calculated from the osmotic pressure of protein molecules present in solution. The number of protein molecules in solution must be relatively small considering the large size of each individual molecule.

It becomes thus understandable that the proteins play a part in the distribution of water in the body under normal as well as under pathological conditions and particularly in edema. Starling and Bayliss especially have appreciated the significance of proteins in this respect. In recent years M. H. Fischer and Eppinger attributed great importance to the rôle which proteins play in the development of edema. But while Fischer had in view mainly the proteins of organs proper, Eppinger attributed the greatest significance to the protein in the interstitial tissue spaces.

In the foregoing we have found two sets of facts which we must correlate with each other. In the first place, the analysis of edema has established the great importance of salts, especially of sodium chloride in the development of this condition, and secondly we have seen that salts interact with the proteins mainly by depressing the attraction of proteins for water or by influencing the precipitation or solution of proteins. For our purpose we have mainly to consider the depressing effect. In this respect ions act differently according as to whether the protein is an anion or kation. In the living organ-

ism the proteins circulating in the body fluids are as far as they are ionized, in combination with kations; they play therefore the rôle of anions; thus it must be assumed that kations depress their water attracting power and the more so, the higher the valency of the kation. We should then expect that sodium, potassium and calcium would all depress the water attracting power of proteins and act favorably in edema. But in reality we notice on the contrary that, in general, sodium has the tendency to increase edema and to prevent the discharge of the edematous fluid; while potassium and under certain conditions even calcium have usually an opposite effect. If, as we have seen, in specific instances calcium may increase ascites we have in this case in all probability not to deal with a direct effect of the ion on proteins. Neither can the effect of colloidal membranes, and particularly of protein membranes, on the movements of water, and the electrostatic forces which come into play in this process, satisfactorily explain the effect of salts in edema, as far as we understand the factors at work in this condition. Again, we must assume that the proteins forming part of the membranes are mainly metal proteinates. Water would therefore have a positive charge and be attracted by anions. Yet we know that in edema the kations are the more important constituent of salts, as far as their influence on edema is concerned. The fact that neutral isotonic salts in general cause a swelling of collagen, does not satisfactorily explain the effect of salts in edema.

It thus becomes very probable that the salts exert their influence on the development of edema essentially independently of the proteins probably through purely osmotic influences, and that the proteins are concerned in the development of edema only in a secondary way; they become of importance only if primary factors regulating the distribution and elimination of water have become faulty. Proteins play therefore, as far as their rôle in edema is concerned, a part somewhat analogous to that played by salts. Neither of these substances initiates edema, but both play a part subsequently in the development of edema.

Proteins are only one of many factors producing an effect on edema, as they are likewise only one of many factors concerned in the normal distribution of water in the body. According to our present knowl-

edge it would be impossible to consider the influence of proteins as the preponderating factor. Whenever in an individual case the particular causes of edema are removed, the edematous fluid is discharged regardless of the amount of protein it contains. Protein can evidently be readily eliminated from the tissue spaces by the normal organism.

XIV. THE SIGNIFICANCE OF HORMONES IN EDEMA

While the significance of salts in the development of edema has attracted the attention of investigators for a considerable number of years, the conception that hormones may also play a part in this process is of more recent origin and it is mainly to the investigations of Eppinger that we owe this addition to our knowledge. Eppinger found that in many cases of edema, especially in edema due to the so-called myodegeneration of the heart, to nephrosis, acute and subacute nephritis and chronic nephritis—provided in the latter cardiac symptoms are not yet threatening, and the non-protein nitrogen in the blood is still relatively low—the administration of thyroid gland may lead to the discharge of the edematous fluid even in cases in which other modes of treatment are ineffective. In normal individuals thyroid does not act as a diuretic, neither does it strengthen the effect of caffeine, but following oral or subcutaneous injection of water or sodium chloride solution, thyroid administration causes a more rapid elimination of both of these substances. On the other hand, after thyroidectomy elimination of these substances is much delayed. Patients suffering from Graves' disease behave like individuals receiving thyroid tablets; myxedematous patients, on the contrary, are comparable to thyroidectomized animals. While in cases of inanition and fever the elimination of sodium chloride is generally delayed, in nephritis and Raynaud's disease it is much delayed only after subcutaneous administration of sodium chloride, but after oral administration it may be normal. In cases of nephrosis on the other hand it is diminished after both subcutaneous and oral administration, while in compensated heart disease it is normal.

After subcutaneous injection of a sodium chloride solution, the elevation in the subcutaneous tissue caused by the injected fluid remains noticeable much longer in nephritic and myxedematous patients

than in normal persons and in persons suffering from Graves' disease. In cases of inanition the elevation disappears soon; yet the fluid and salt are retained in the body. Subcutaneous injection of hypertonic salt solution leads to the appearance of protein in the fluid and this is probably the cause of the delayed absorption of such a solution. In thyroidectomized dogs protein becomes mixed with the fluid even after injection of an isotonic sodium chloride solution, and this may be also in this case a contributory factor in the slow absorption, as in other cases in which a deficiency in thyroid activity is present.

After hemorrhage a fluid, relatively poor in protein and rich in sodium chloride, moves from the tissues into the blood. In thyroidectomized dogs and in myxedematous persons this movement is delayed. Under the same condition fluid enters the blood and dilutes it also in cases of nephritis, but subsequently sodium chloride is retained in the blood-vessels.

Eppinger interprets these facts as follows: In conditions which lead to edema or myxedema, the permeability of the blood-vessels is increased. In consequence of this alteration the fluid in the interstices of the tissues is richer in protein than usual. This leads to the retention of water and sodium chloride in the tissues and thus to edema. Administration of thyroid causes an increased cell metabolism and in consequence the cells destroy more actively the proteid which collects in the tissue spaces; thus this cause of edema is eliminated. In general Eppinger assumes in agreement with Asher's theory of lymph formation that conditions which increase organactivity increase thereby the quantity of lymph and the elimination of interstitial fluid in the affected area.

Whatever the correct interpretation may be, there is no doubt about the marked effect of thyroid on the distribution of fluid in the body. In experiments which Hoover carried out in our laboratory several years ago he found that in guinea pigs suffering from marked inanition a certain amount of fluid usually collects in the peritoneal cavity, while it is absent in the large majority of animals in which the same or even a greater amount of inanition has been produced through the combined effects of thyroid feeding and a diminution in the intake of food. It is furthermore very probable that thyroid substance acts primarily not on the kidney but on the intermediary distribution

of salts and water; in a similar manner we found previously indications that caffeine does not influence salt and water movements exclusively through its effect on the kidney. Other observations likewise agree with Eppinger's findings. Thus Ruchti found that thyroidectomy in rabbits not only diminishes the amount of carbon dioxide but also the amount of water given off in the respiratory air, and that a simultaneous thymectomy intensifies and prolongs this effect. Of interest in connection with Eppinger's observations, are likewise the findings of Tatum, that complete thyroidectomy in young rabbits may lead, among other changes, to a hydropic condition in heart, liver and kidney cells. This may be followed by a more general interstitial edema and ascites, which latter Tatum considers as secondary to weakness of the heart action.

The result observed by C. Hart and E. Uhlenhuth, that tadpoles fed with thyroid gland become edematous, is probably due to conditions of a different character. According to Hart it is brought about by degenerative processes which take place in the thyroid gland in such larvae. The condition in the larvae is therefore in certain respects analogous to the myxedematous condition in the fully developed organism.

We may also refer to the findings of Deutsch that in myxedema the concentration of proteins in the blood is increased and that thyroid feeding diminishes it. These findings might be taken to support Eppinger's interpretation of the action of the thyroid in edema.

Quite recently however some interesting facts have been published which suggest a different interpretation of the action of the thyroid on the movement of water and its influence on edematous fluid. Ellinger showed that substances which increase the elimination of water, like thyroid gland, caffeine and certain salts, diminish the attraction which proteins exert on water; they reduce the "imbibition pressure" of proteins and thus make water available for excretion through the kidney. Ellinger demonstrated this effect in experiments in which he perfused the Laewen-Trendelenburg frog preparation with various fluids and also through ultrafiltration.

Of still greater significance are perhaps experiments carried out by Embden and his associates, which indicate that thyroid extract, when added to certain solutions, increases the rapidity with which the

latter pass in vitro through a membrane of frogskin. A substance given off by the thyroid gland may therefore apparently increase the permeability of membranes and for this reason accelerate the elimination of fluid from the tissue spaces. Recent experiments in Asher's laboratory in which it was shown that, under the influence of thyroid, methylene blue passes more rapidly from the body fluids into glandular structures in the membrane nictitans of the frog, suggest a similar interpretation. Thyroid substance would thus have an effect opposite to that of calcium chloride and adrenalin.

It is probable that substances present in other glands with internal secretion also exert an influence on the distribution and elimination of water. In this connection we have to consider especially the posterior lobe of the hypophysis, which affects not only the secretion of urine, but also the elimination of water through the wall of the stomach. E. Pohle found that in frogs in which the hypophysis has been extirpated, both the elimination of fluid through the kidney and the taking up of water through the skin is diminished. In consequence of this disturbance in the exchange of fluid, hypophysectomized frogs become edematous; there is noticeable not only a marked edema of the skin, but in addition the lymph spaces are filled with water. Pohle assumes therefore that the secretion of the pituitary gland affects the exchange of water in general.

In agreement with this conclusion is the effect of pituitary extract on the exchange of water in diabetes insipidus, where it not only diminishes the excretion of fluid but increases the elimination of sodium chloride through the kidney, and therefore the concentration of the urine; but in addition it affects the intermediary exchange of water. As we have stated above, in diabetes insipidus, under the influence of pituitrin, water leaves the blood and perhaps also the lymph vessels and enters the tissue spaces. The effect of pituitrin is therefore analogous to the action of caffeine in nephrectomized animals, which we have discussed previously.

Yet there is no indication that pituitrin increases the permeability of blood-vessels. On the contrary Krogh and Rehberg demonstrated the opposite effect of pituitrin. According to these authors if the legs of frogs are perfused with Ringer's solution, to which has been added 3 per cent gum arabic and red corpuscles, under the influence

of this solution the tonus of the capillaries is lost, the capillaries dilate and pari passu their permeability increases and the perfusion fluid leaves the vessels. If now a very small amount of pituitrin is added to the perfusion fluid the tone of the vessels is restored and the permeability again becomes normal. Previously Krogh and Harrop had shown that under normal conditions the blood serum contains a substance which maintains the capillary tonus. Krogh and Rehberg have made it seem very probable that the internal secretion of the pituitary gland is the substance which functions in this way.

Other parts of the nervous system may also influence the movements of water. They act, according to Pohle, mainly through their effect on the circulation; dilatation of the blood-vessels in the skin and kidney following, for instance, the section of the anterior nerve roots of frogs, leads to increased absorption of water through the skin and to increased elimination through the kidney.

In conclusion we may state that various substances of a hormone character influence the exchange of water and salts not only between blood and kidney, but also between tissues and blood, and that under certain conditions such substances may even reverse the direction of the movement of salt and water. Intimately connected with this effect on the movement of water and sodium chloride is the effect which the thyroid hormone exerts on the elimination of a localized, experimentally produced excess of fluid, in cases in which pathological changes exist that tend to the development of edema. Under these conditions certain hormones may likewise accelerate the absorption and elimination of an excess amount of fluid.

XV. THE COMPOSITION OF EDEMATOUS FLUID

In this chapter we wish to discuss very briefly some of the more important facts, bearing on the chemical constitution of edematous fluid.

Qualitatively the constituents of the edematous fluid are similar to those of the blood, but quantitatively some interesting differences are found. We have mentioned previously that the amount of protein in the edematous fluid differs according to the disease in which edema develops. In general the percentage of protein is higher in inflamma-

tory edema than in edema caused by venous obstruction, but considerable variations occur in individual cases. In edematous conditions of the skin the protein content in inflammatory lesions is likewise higher than in non-inflammatory lesions. It seems that in inflammatory processes the amount of globulin and especially of euglobulin is, at least in some cases, higher in the edematous fluid than in non-inflammatory cases. We have already in a previous chapter considered in greater detail the protein content of certain non-inflammatory edematous fluids.

According to various authors the sodium chloride concentration is frequently greater in the edematous fluid than in the blood. This applies to the renal and cardiac edema of man as well as to the edematous fluid in uranium nephritis in rabbits. It seems that at the time when the discharge of the edematous fluid begins, the sodium chloride is eliminated in larger quantities from the edematous fluid than from the blood; at that period the concentration of sodium chloride may become temporarily greater in the blood serum than in the edematous fluid. In a similar way the edematous fluid in war edema is, according to Hülse, richer in sodium chloride than the blood. This author furthermore finds that in edema due to undernourishment, administration of sodium bicarbonate leads to an increase of this substance in the peritoneal transudate simultaneously with an increase in sodium chloride. He assumes that sodium bicarbonate pushes the sodium chloride into the tissues in a direction contrary to the osmotic potential.

It must be stated however that the majority of these conclusions suffer from the fact that they are based merely on chloride determinations, it being assumed that sodium and chloride ions are always present in equivalent amounts. As we shall see below this does not altogether hold good. Various authors have recently determined the sodium separately from the chloride. Thus Blum, Aubel and Hausknecht showed that the concentration of sodium is increased in the ascitic and in the edematous fluid in general as compared with that of the blood. Whenever the kidney does not permit a sufficient elimination of sodium to take place, it passes into the peritoneal fluid and, according to these authors, the movement of sodium determines always a parallel movement of water.

Various authors have attempted to explain the difference in the distribution of sodium chloride in the blood serum and in the ascitic fluid. Thus Rona at first referred it to the different concentration of proteins in the blood and in the edematous fluid. He assumed that only water can serve as a solvent for the sodium chloride; and the protein content, being greater in the blood than in the edematous fluid, less water would be available in the former for the solution of the salt; the concentration of sodium chloride would thus be greater in the ascitic fluid than in the blood serum. This interpretation presupposes a variation in the concentration of sodium chloride in edematous fluid inversely proportionate to the concentration of protein. In subsequent studies of the distribution of the sodium and chlorine ions, in case blood serum is separated by a membrane from distilled water or from a diluted solution of electrolytes in water, Rona and György concluded that in the blood serum about 10 to 15 per cent of the sodium is combined with protein in the form of a sodium proteinate solution and that if the hydrogen ion concentration of the solution is on the acid side of the isoelectric point of the protein, a salt is formed in which the protein is the kation. Thus an unequal distribution of the diffusible ions occurs on both sides of the membrane corresponding to Donnan's membrane equilibrium. Inasmuch as in normal serum we have to deal with a Na proteinate solution, there would be inside the membrane a greater concentration of chlorine ions.

It is of interest to compare with these conclusions of Rona and György the recent findings of R. F. Loeb, Atchley and Palmer. These authors determined the relative values for sodium and chlorine in blood serum and in edematous fluid and they found the chlorine ion to be more concentrated in the edematous fluid, while the concentration of the sodium was approximately the same in both the blood serum and the edematous fluid. The concentration of calcium was also the same in both, but potassium showed throughout a higher concentration in the blood serum. In accordance with the expectation the differences in the concentration of the chlorine ion in the serum and in the ascitic fluid were inversely proportionate to the concentration of the proteins in both fluids. These are to our knowledge the first comparative determinations of potassium in the blood

serum and in the edematous fluid and the constant difference in the distribution of this substance in these two fluids is of great interest. A definite membrane equilibrium seems thus to exist between chlorine and protein on the one hand and potassium and sodium on the other hand in the edematous fluid and the blood serum; and this equilibrium does not depend upon vital tissue activities, inasmuch as it remains unaltered, according to the same authors, if the two fluids are separated in vitro by a collodion membrane.

The osmotic pressure of the edematous fluid is about the same as that of the blood serum or only a little lower (Bottazzi, R. F. Loeb, Atchley and Palmer). Lymph, on the other hand, has a higher osmotic pressure than blood serum (Hamburger), and organ extracts have a still higher osmotic pressure. According to Collip, non-electrolytes are concerned in the high osmotic pressure of organ extracts to a greater extent than in the case of the body fluids. Sugar, urea and non-protein nitrogen in general are present in similar concentrations in edematous fluid and in blood serum (Denis and Minot, R. F. Loeb, Atchley and Palmer). However, the recent investigations of Otto Klein have made it seem probable that in certain cases of cardiac and renal edema non-protein nitrogen may accumulate in the edematous fluid. According to Jansen the tissue fluid and blood serum have likewise an equal concentration of non-protein nitrogen and also of sodium chloride. In edematous persons suffering at the same time from gout, uric acid varies in equal ratios in blood serum and edematous fluid (Beckmann, Thannhauser), but the concentration of this substance may be greater in the blood serum (Thannhauser).

Palmer, Atchley and R. F. Loeb have shown that the conductivity of the edematous fluid depends upon its protein content. According to these authors protein near the isoelectric point lowers the conductivity while protein, when combined with acid or alkali to form a salt, increases the conductivity. Inasmuch as at the hydrogen ion concentration of the edematous fluid a great part of the protein is non-ionized, the conductivity of the edematous fluid decreases concomitantly with an increase in proteid content. It varies therefore in different kinds of edema in contradistinction to osmotic pressure which is rather constant. The hydrogen ion concentration of edematous fluid and of normal subcutaneous tissue fluid is similar to that

of blood serum. Likewise the concentration of the HCO_3 is the same in edematous fluid and in blood serum (R. F. Loeb, Atchley and Palmer). On the other hand, if excessive work leading to exhaustion is done, the fluid in the spaces separating muscle fibers becomes acid (Schade). In the pus of acute inflammation also we find what Schade calls a hydrogen hyperionia, the pH being on the acid side; this is accompanied by increased carbondioxide tension and a diminished power of the fluid to bind carbondioxide. These facts will be of interest in considering the possible rôle of hydrogen ion concentration in the development of edema. We shall discuss this problem in the next chapter.

If we inject intraperitoneally into normal rabbits a 0.85 per cent solution of sodium chloride the osmotic pressure of this fluid becomes higher than that of the blood in the course of a few hours (Fleisher and Loeb), but we found that if we inject the same fluid into rabbits which have previously been nephrectomized or which have received an injection of uranium nitrate one or three days previously, or in which merely an incision has been made into the thoracic wall, the osmotic pressure is higher in the blood than in the peritoneal fluid at a corresponding period of time. In normal animals which have received an intraperitoneal injection of a sodium chloride solution, other substances than sodium chloride move probably from the blood into the peritoneal cavity, in accordance with the higher concentration of these substances in the blood. This movement occurs apparently at a more rapid rate than the reverse movement of sodium chloride. In animals which have received uranium nitrate three days previously the normal exchange of substances between blood and peritoneal cavity is interfered with, as we have shown in a preceding chapter.

As we have stated above membrane equilibria, which are due to the unequal distribution of protein salts on both sides of the membranes separating edematous fluid and blood and lymph, play also a part in determining the concentrations of various ions in the edematous fluid as compared with blood and lymph. A definite membrane equilibrium is presumably likewise established between the edematous (or interstitial) fluid and the organ content; in this case the cell boundaries play the rôle of the separating membranes.

XVI. EDEMA AND ACIDOSIS

The term acidosis may signify either of two conditions, (1) a change in the buffer system of the blood towards the acid side; such a change leaves the hydrogen ion concentration of the blood unaltered, or (2) a change in the hydrogen ion concentration of the blood in the direction towards the acid side. There is therefore a certain ambiguity attached to the term acidosis which could be avoided in either of two ways. The first of the two conditions mentioned might be designated as a diminution in the blood alkali or as an increase in the H_2CO_3 of the blood; either of these two changes is compensated for through secondary mechanisms in such a way that the hydrogen ion concentration of the blood remains unchanged. The second condition would then represent a true acidosis in which the hydrogen ion concentration of the blood is actually increased. Or secondly we might distinguish between a compensated and an uncompensated acidosis.

The term acidosis was first used at a time when these various possibilities in the regulation of the hydrogen ion concentration had not yet been sufficiently analyzed; at that time a diminution in the alkali reserve of the blood due to an increase of the acids in the circulating body fluids was the condition generally called acidosis. According to L. Henderson the ratio $BHCO_3 : H_2CO_3$ is a measure of the hydrogen ion concentration of the blood. On the whole subsequent determinations have confirmed this conclusion, although this ratio may perhaps only be approximately correct. An increased hydrogen ion concentration in the blood may be produced through an increased production of acid in the body, through an increased introduction of acid into the body from the outside, through a diminished elimination of acid from the blood, or through a decreased elimination of acid through other channels, in particular of carbon dioxide through the lung. Secondarily perhaps the elimination of acid through the glands of the skin, intestines may also play a part.

In the opposite way also an alkalosis may be produced in the blood; but in general any change tending to alter the hydrogen ion concentration of the blood cells calls forth counter-reactions which tend to neutralize the primary changes. Thus various possibilities of compensation exist which have been analyzed only in the last few

years, in particular by Yandell Henderson and Haggard and by Van Slyke.

The differentiation between compensated and uncompensated acidosis means an advance in our understanding of the changes in the blood; but it appears that this analysis will have to be extended in still another direction. So far almost exclusively the changes which take place in the hydrogen ion concentration and in the buffer system of the blood have been considered; this is sufficient, as far as certain functions, like the mechanism of respiration, are concerned; but it is insufficient in other respects, especially when problems of edema are considered. In this case we want to know whether or not the changes in the tissues take a course parallel to those in the blood. Now the compensatory changes in the blood may take place in either of two ways: (1) The excess of acid or alkali may be removed from the blood through excretion into the urine, into the air of the lung, or into the intestines. In this case the acid is practically eliminated from the body; or, (2) the excess of acid or alkali may be transferred to either blood cells or tissues. Compensation is accomplished in both cases equally as far as the blood is concerned; but as far as the condition of the tissues and the organism as a whole is concerned, there is a difference. In the latter case the hydrogen ion concentration of the blood may have become normal, while the hydrogen ion concentration of the organism as a whole remains unchanged and in the hydrogen ion compensation in certain tissues or cells, even an actual decompensation may have taken place at a time when compensation is accomplished in the blood and both effects may be the consequences of the same mechanism. It might therefore be advisable not only to distinguish between compensated and uncompensated acidosis, but also to distinguish between compensation through elimination and compensation through shifting of acid or alkali within the organism.

However, at the present time our knowledge as to the hydrogen ion concentration outside the blood is very fragmentary. We know through the determinations of Michaelis, Schade, Neukirch and Halpert and others that the hydrogen ion concentration in the muscle is slightly greater than in the blood, and that during work it may in this tissue change even to the acid side, and that the connective tissue juice has a hydrogen ion concentration which is above that of

the blood, although it is still on the alkaline side. We may assume that directly around the active cells and tissues the hydrogen ion concentration is somewhat greater than in the blood and that it decreases with increasing distance from the tissues, as a result of the diffusion of the acid products. Inasmuch as the content in non-diffusible ions differs in the blood and in the interstitial fluid, there will be presumably a slight increase in the concentration of hydroxyl ions outside of the vessels; this would tend to counteract to some extent the greater concentration of carbon dioxide and perhaps of other acid products outside the vessels.

As far as our analysis of edema is concerned, it is of importance that the reaction in the blood, as well as in the interstitial fluid, is still on the alkaline side and that accordingly the proteins as far as they are combined are not acid protein salts but alkali protein salts; furthermore, that the actual changes in hydrogen ion concentration, which have been found in non-inflammatory body fluids, are very small and do not, as far as we know, suffice to make the body fluids acid in conditions which lead most frequently to edema. The changes in potential or actual hydrogen ion concentration, in conditions which may lead to edema, have been studied in decompensated heart disease and in nephritis and we must therefore consider the principal results obtained in these diseases.

In cases of cardiac decompensation the arterial blood (Harrop) as well as the venous blood (Lundsgaard) may show unsaturation with oxygen. This is partly due to insufficient oxygenation of the blood in the lungs and partly to the slow circulation of the blood in the capillaries which leads to a more complete absorption of the oxygen from the blood. Yet this deficiency in oxygenation may be compensated for by an increased respiratory minute volume and in consequence of this compensatory process the oxygen consumption per unit of body surface may even exceed that found in normal individuals and the respiratory quotient may be normal (Peabody, Wentworth and Barker). In cardiac decompensation the most marked change which may affect the acid-base equilibrium in the blood consists in a relative retention of carbon dioxide in the blood associated with a low carbon dioxide content of the alveolar air. Therefore the carbon dioxide tension in the alveolar air is low in proportion to the

carbon dioxide tension in the arterial and venous blood (Peters and Barr). According to the last named authors the carbon dioxide tension in the alveolar air is lower than normal as compared with the plasma bicarbonate in cardiac decompensation and in dyspnea; in these cases the efficiency of the lung as a means for the oxygenation of the blood and the elimination of carbon dioxide is greatly reduced. In addition the slowing of the capillary circulation may also play some part as stated.

While there is thus a relative increase in carbon dioxide tension in the blood, the absolute values usually fall within the normal range. It is not always possible to determine how in these cases an uncompensated acidosis due to a relative surplus of carbon dioxide in the blood does occur, because certain individual differences, which are constant in a given person, seem to exist in the carbon dioxide: plasma bicarbonate ratio. A condition which would represent an uncompensated acidosis in one individual, might fall within the normal range in another. However, in some cases such an uncompensated acidosis does occur. In addition in some patients an absolute deficit in the blood alkali was observed; this again led in certain cases to an unpensated acidosis owing to lack of sensibility in the respiratory center.

The conditions found in cardiac decompensation seem to differ from those observed by Means, Bock and Woodwell in pneumonia, where, according to these authors, there exists an acidosis due to retention of carbon dioxide unaccompanied by a lowering of the alkali reserve. We may thus conclude that in cardiac decompensation the hydrogen ion concentration in the blood is in most cases either within the normal range or only slightly above this range. It is not conceivable that this change in pH can alter the colloids in the tissue spaces in such a way that edema follows. We shall return to this point in the next chapter.

In nephritis determinations of the alkali reserve by various investigators have shown a diminution in many cases (von Hoesslin, Sellards, Goto, Peabody, Meyers). Especially in cases of uremia the decrease in the blood alkali was marked. Rieger and Freund measured the amount of hydrochloric acid necessary to cause hemolysis in the blood of nephritics. They found this amount diminished in all cases of nephropathy accompanied by tubular and glomerular lesions; in

these cases there was no rise in blood pressure but a tendency towards retention of sodium chloride and towards the development of edema. They concluded that in these patients a diminution in the blood alkali occurs at a very early date. In cases of vascular nephropathy, on the other hand, where the blood pressure is high, with or without nitrogen retention and without a tendency to edema, there is no diminution in alkali reserve.

In dogs which had been poisoned with uranium nitrate or in which the uereter had been occluded, Elmendorf noted a diminution in the blood alkali and similarly McNider found in dogs affected by spontaneous nephropathy, or in cases of uranium poisoning, either a decrease in the blood alkali or at least a diminished power to reëstablish the normal alkali reserve after injection of an acid or a base into the animal, or after chloroform anesthesia.

According to McNider there exists a certain parallelism between the degree of diminution in the blood alkali and the severity of the pathological changes observed in the kidney in experimental nephritis. He furthermore found that injection of sodium bicarbonate may diminish the pathological effects of uranium poisoning in rabbits or of chloroform anesthesia in nephropathic dogs. This would indicate an etiological relationship between the diminution in the blood alkali and the development of kidney lesions. On the other hand, according to Karsner, Reimann and Brooks, the diminution in alkali reserve does not precede the kidney lesions. It had also previously been maintained by von Hoesslin and M. H. Fischer that the administration of sodium bicarbonate tends to decrease the albuminuria and to diminish the kidney lesions. However, while in some cases the administration of alkali may perhaps act favorably, on the whole clinical experience does not tend to substantiate the conclusion that sodium bicarbonate is particularly efficient in the treatment of nephritis. However, we shall refer below to some facts which indicate that in certain cases administration of alkali may be of some benefit in nephritis.

As to the causes of this diminution in blood alkali in cases of nephritis, the evidence points strongly to the conclusion that the kidney lesion is the primary factor which secondarily leads to a retention of acid in the blood. Greenwald has shown that in cases

of diminished alkali reserve in nephritis there is an increase in the inorganic phosphorus in the blood. Mariott and Howland found that this increase is due to the retention of acid phosphate and that the retention is caused by the inability of the diseased kidney to excrete this substance properly. These findings were confirmed by Feigl as well as by Denis and Minot. The latter found in 65 per cent of cases of nephritis a retention of inorganic phosphorus in the blood plasma, which becomes especially pronounced in cases which end fatally.

While usually in cases of increased acid production ammonia is formed in excess in order to neutralize the surplus of acid, in the alkali depletion found in nephritis such an excess of ammonia is lacking. The recent investigation of Nash and Benedict may perhaps explain this difference in the behavior of ammonia in various conditions in which a diminution in blood alkali is found. These authors have made it seem probable that ammonia is produced as a result of the activity of the kidney tissue. Perhaps the diseased kidney has lost entirely, or in part, the power to produce ammonia and thus the difference between nephritic diminution in blood alkali and the corresponding change in other conditions may be explained. The results of Mariott and Howland suggest that the retention of acid phosphate is the cause of the alkali diminution in nephritis, and thus the actual or potential acidosis would be rather the result than the cause of the nephritis. While this conclusion is probably essentially correct, still the acidosis as such may perhaps contribute to the inability of the kidney to excrete sufficiently the acid produced and in this way a vicious circle may be established.

The findings of Straub are also confirmatory of the view that the disturbed renal function leads to alterations in the composition of the blood, and at the same time support the suggestion made above as to the function of alkali. He finds that while the normal kidney is able to regulate the elimination of acid and alkali taken up with the food in such a manner that the hydrogen ion concentration of the blood remains constant, the diseased kidney is no longer able to excrete a surplus of acid or it can accomplish such an elimination only if at the same time alkali is given. Straub finds likewise a great variability in the anions present in the serum of nephritic individuals

in contradistinction to the constant composition of the normal serum. The character of the anions present in such cases depends to some extent upon the anions taken in with the food. Nephritic patients have lost the power of keeping constant, through excretion, the constitution of the blood in inorganic ions. It is therefore possible that other anions besides the phosphates are implicated in the retention of acid in the blood.

The evidence which we have presented so far, and similar observations by Means and Rogers, as well as by Barr and Peters, prove conclusively that the diminution in the alkali of the blood is an early result in nephritis; furthermore the origin of this diminution has been established. However, these investigations do not give us any information as to the actual hydrogen ion concentration of the blood and from our point of view the question, whether this concentration is increased in nephritis, is perhaps the most important one. The diminution in blood alkali due to the retention of non-volatile acids might be compensated for either by the movement of alkali from tissues to the blood, or by a diminution in the carbon dioxide tension of the blood. Recent investigations show that such a compensation frequently occurs. Thus Peters, Barr and Rule found in a case of chronic nephritis with hypertension the alkali value of the blood at the lowest value of the normal range; yet the hydrogen ion concentration of the blood was normal. H. Straub in an extensive study has recently shown that in many cases of renal disease the hydrogen ion concentration of the blood remains unchanged, although the carbon dioxide binding power of the blood is diminished; in such cases compensation was accomplished through an increased elimination of carbon dioxide in the lung. In other cases, however, there is according to Straub an increase in hydrogen ion concentration, but—and this is important from our point of view—without a corresponding tendency towards the development of edema in such individuals. Means, Bock and Woodwell likewise observed a nephritic patient with low blood alkali and decompensated acidosis. The evidence thus far at hand points then to the conclusion that no definite relation exists between an increase in the hydrogen ion concentration of the blood in heart and kidney disease and edema. In the following chapter we shall find further evidence sustaining this conclusion.

XVII. THE LOCALIZATION OF EDEMA AND ITS BEARING ON THEORIES OF EDEMA

Within the last decade a conception of edema has been the subject of much discussion, which differs from previous theories in that it assumes that the seat of edema is not, as had been previously believed, mainly the interstices of the connective tissue, the lymph spaces and the serous cavities, but rather the cells and parenchyma of the various organs. This theory furthermore assumes that the cause of edema is not, as had hitherto been conceived, a change in the condition of the walls of the blood and lymph vessels, nor an alteration in the mechanics of the circulation, nor is it a change in the physio-chemical relation between the fluid in the blood and lymph vessels on the one hand, and the fluid in the surrounding interstitial spaces and in the serous cavities on the other hand, but that the cause of edema is an alteration in the physico-chemical relation between the circulating fluid and the parenchyma of the organs. It is furthermore assumed that this alteration is due to a pathological condition in the metabolism of the parenchyma. Following an injury chemical changes are supposed to occur in the cells or parenchymatous tissue in general, as a result of which water is drawn to the organs from the surrounding circulating fluid. Lazarus-Barlow as early as 1895 expressed the view that anemia in the tissues is responsible for edema following circulatory disturbances. He believed that under this abnormal condition the tissues needed an increased amount of fluid and that the resulting edema represented thus an adaptive process, comparable in that respect to inflammation, which likewise has the characteristics of an adaptive process. Edema was said to bring about a dilution and elimination of the injurious waste products of metabolism. In this connection we may mention that a somewhat similar effect has been attributed to edema by more recent authors who, like Widal, have pointed out that edema and uremia are to some extent mutually exclusive and who attributed thus to edema a certain detoxicating function. In a similar manner Lazarus-Barlow explained edema of the lung as well as inflammatory edema; renal edema also he attributed partly to the retention of waste products in the tissues.

While teleological viewpoints were prominent in the conceptions of Lazarus-Barlow, the parenchymatous theory of edema, free from such considerations and based merely on physio-chemical findings, was first expressed by Jacques Loeb in 1898. This author found that excised frog muscle could be made to take up an increased amount of water if acid or alkali was added to the solution of sodium chloride into which the muscle had been immersed. He assumed that the acid caused an increase in osmotic pressure in the muscle and thus led to edema. Subsequently he applied these observations and conclusions to edema in general. According to his view edema is found under various conditions of cell or organ injury, which have all in common an interference with the processes of oxidation. In consequence of these interferences acid is produced in the cells, and this leads to physico-chemical changes within the cells or tissues and especially to an increase in osmotic pressure. Edema is the result of these changes. Even pulmonary edema he supposed to be due to this mechanism. All edema can be exemplified in the swelling which takes place in a ligated frog leg immersed in water below the place of ligation. Here the tissues take up water as the result of the production of acid, which, in conformity with the conclusions of Araki, is called forth by the lack of oxygen. Jacques Loeb considered the state of the cell colloids as an important factor in determining the amount of water attracted by the cells. He showed that potassium salts cause a greater swelling of muscle than sodium salts and he compared this effect with the affinity of potassium soaps for water.

However, this author very soon reached the conclusion that this theory of edema was not in harmony with a number of important facts and he therefore abandoned these conceptions, the hypothetical character of which he had recognized from the beginning. Very similar ideas were soon afterwards expressed by Martin H. Fischer who attempted to substantiate them in a series of experiments dealing mainly with the affinity of colloids for water; in fact in contradistinction to his predecessor, he emphasized the rôle of organ colloids, the swelling of which under the influence of acid he considered as the main source of edema. Fischer also bases his theory largely on experiments with the frog leg and adopts the conception that lack of oxygen, leading to acid formation within the cells or

tissues, is the initiating factor in edema. He likewise explains pulmonary edema on this basis. He differs, however, in one important respect from the views of Jacques Loeb. While the latter assumed that the production of acid leads to an increase of osmotic pressure within the cell or organ parenchyma in general, Fischer believes that the acid acts on the cell colloids and increases their affinity for water in a manner similar to that of gelatin or fibrin, a conclusion in harmony with the experiments of Spiro, and others, who have shown that acid can cause a swelling of these proteins.

Alkali, pyridin, urea, amins and similar substances may likewise increase the affinity of colloids for water, but in actual edema, acid formation in the organs is the essential cause of the edematous swelling. Edema is then essentially a problem of the hydration of cell colloids; and the production of acids, through lack of oxidation, is the main cause of this increased hydration. Other substances may perhaps occasionally come into play, but they are, to say the least, of minor significance. All varieties of edema, wherever it is situated, whatever its apparent clinical origin, are to be explained in a similar manner. This applies equally to cardiac, renal and pulmonary edema; it also applies to edema of the brain, to inflammatory edema and toxic or anemic edema. It furthermore applies to glaucoma which, according to Fischer, consists in a swelling of the colloids of the eye. Any condition that causes swelling of gelatin or fibrin or of the frog-leg, when it is deprived of its circulation, may cause edema; and similar conditions in the eye cause glaucoma.

Edema of the serous cavities, or of the interstitial connective tissue is merely due to secondary changes, which are comparable to alterations observed in colloids in the gel state; they may gradually retract and during this process press out water (syneresis); the water, thus set free through secondary changes in the primarily edematous organs, accumulates in the serous cavities and this process causes ascites, hydrothorax and hydropericardium.

The swelling caused in colloids through acid or alkali can be counteracted by the addition of various neutral salts, and this dehydrating effect of salts shows a gradation similar to that previously found by Hofmeister, varying in accordance with the effectiveness of the ions constituting the salts. Citrates, tartrates, acetates, phosphates and

sulphates gave an especially marked dehydrating effect on colloids and are therefore according to Fischer most effective in the treatment of edema. But all neutral salts, especially in hypertonic solutions, have this effect and may therefore be recommended in the treatment of edema; dehydrating salts in particular may benefit glaucoma, if injected under the conjunctiva. In addition administration of an alkali is to be recommended in order to neutralize the acid, which this author believes to be responsible for the swelling of organ colloids.

The main difference between the earlier conceptions and those of M. H. Fischer concerns the character of living cells and the exchange of substances between the latter and the surrounding fluid. While Jacques Loeb assumed that cells are surrounded by a protoplasmic membrane which possesses a selective permeability, Fischer on the contrary denies the existence of such a limiting membrane and believes that the cell colloids are immersed directly in the body fluids and are therefore subject to the same laws of swelling as gelatin and fibrin.

Various objections can be raised to these conceptions of edema, and we shall briefly discuss the principal ones:

1. The seat of edema is primarily not the parenchyma of organs but the interstitial tissue. All direct observations point to this conclusion which has again been maintained more recently by pathologists like Marchand, Klemensiewicz, Lubarsch and others. Hülse, who, like Fischer, believes that the cells and parenchyma in general are primarily affected, does not give definite facts in support of his contention.

In the case of acute pulmonary edema in rabbits, produced through the intravenous injections of adrenalin, it can be clearly shown that fluid is pressed out from the blood-vessels into the interstitial spaces and alveoli of the lung. The conditions under which this occurs are not compatible with the assumption that the edema is due to changes in cells or even in connective tissue fibrils composing the lung tissue which would lead to an attraction of water. Moreover in edema of the skin the spaces between the connective tissue fibrils are primarily affected and not the fibrils as such. In experimental edema, produced in rabbits through the intravenous injection of a solution of sodium chloride, the edema originates in the serous cavities and in the in-

terstitial spaces of the connective tissue around the pancreas and salivary glands, and not in the parenchyma of organs. These and other observations make impossible the interpretation of these edemas as comparable to the pressing out of water from gels (so called syneresis). The edematous condition of the cells proper and of the parenchyma in general is usually a secondary phenomenon.

As we have mentioned above, in certain cases fibrillar structures as well as cells may become edematous. This applies also to the hydremic plethora, produced experimentally in rabbits, where for instance, the secreting cells of the salivary glands may take up fluid (Wertheimer and Battez); we have every reason for believing that this is a process secondary to the interstitial edema, which is more marked than that of the tissue constituents. The abnormal environment in which the cells are placed, as the result of the interstitial edema, and the movement of an abnormal fluid through the gland proper into the gland ducts are probably responsible for an injury of the cells and the subsequent imbibition of fluid. This condition is perhaps comparable to changes in red blood corpuscles which have been observed by Prigge after intravenous injection of an hypertonic solution of sodium chloride into patients suffering from pneumonia. He finds that while usually after such an injection fluid is given off by the corpuscles to the surrounding medium in accordance with the laws of osmosis, sometimes the reverse process may occur and the injured corpuscles may take up fluid from the blood. Thus an edema of the erythrocytes may occur which is secondary to the hydremic condition of the surrounding medium.

2. There is no reason for assuming that the formation of acid in the tissues is the essential cause of edema. We have already considered in the preceding chapter the formation of acid in conditions leading to edema, and concluded that while there may be an increase in the hydrogen ion concentration in the circulating blood in certain cases of cardiac decompensation and in kidney lesions, it is slight and no parallelism is apparent between this increase in hydrogen ion concentration and the development of edema.

We shall now discuss under what conditions the production of acid in the body might lead to the formation of edema. We must distinguish between acid production in the circulating body fluids

(blood and lymph) and that in the interstitial fluid, which is temporarily held in the spaces surrounding the various cells and tissues. In the former there are present two factors which tend to antagonize the effect of an increase in the concentration of acids, namely, special buffer substances and salts in general. The buffer mechanisms tend to oppose the deviation in the ratio of the fluid towards the acid and alkali side and would make necessary the addition of considerably greater amounts of acid and alkali in the living organism than in the in vitro experiments. This point has been especially emphasized by Lawrence Henderson and E. J. Cohn and by Bayliss. As to the second factor, the neutral salts present in the body would tend to oppose the acid and alkali effect of proteins, as has been pointed out by A. R. Moore. But even if at last these mechanisms have been overcome, then another factor would come into play which in the living organism would prevent the production of edema under the influence of acid. In the circulating body fluids a certain proportion of the proteins are in all probability present as alkali-proteinates. As such they would tend to bind a certain amount of water. Now, if free acid came in contact with these substances, the acid would first convert some of the alkali proteinates into isoelectric proteins. Instead of increasing the water binding power of the proteins, this process, on the contrary, would decrease it. The addition of considerably greater quantities of acid would be required in order to produce a conversion of the isoelectric protein into protein-acid combinations, in which the protein would be the kation and the anion of the acid molecule the anion. Under these conditions the water binding power might reach again its original level and might gradually surpass it.

But is is not conceivable that the slight alterations in hydrogen ion concentration, which have been observed in the blood plasma, would be sufficient to bring about so far going changes and it is doubtful if such changes would be compatible with the necessary functions of respiration and tissue metabolism.

As far as the interstitial fluid is concerned, we have reason for assuming that the hydrogen ion concentration is here slightly higher than in the circulating body fluid; but a constant exchange of substances between these two kinds of fluids would tend, even in the tissue fluid, to keep changes in hydrogen ion concentration within

very narrow limits and the proteins would presumably still remain slightly on the alkaline side. Likewise in the tissue spaces buffer substances and salts again would tend to counteract an acid effect on proteins. The conditions present in the tissue fluids would therefore in principle be similar to those obtaining in the blood and lymph.

As far as the cells are concerned, which are surrounded by the interstitial fluid, we have shown that a slightly acid reaction in their environment may, under certain conditions, not only not lead to edema of the cells, but on the contrary tend to increase the consistency of the cells and thus to prevent the entrance of water into the parenchyma proper; in this way acid may in some cases promote rather than diminish certain cell activities.

That thus in the interstitial tissue acid cannot be the cause of edema in the majority of cases, is also proven by the hydrogen ion concentration of edematous fluids which have been found not to differ much from that of the blood. Even in the inflammatory edema produced through the instillation of mustard oil into the conjunctival sac in rabbits, Hirschfelder found the reaction of the edematous fluid to correspond to a pH of 7.2 to 7.5 which is close to the alkalinity of the venous blood. Schade likewise finds the hydrogen ion concentration of edematous fluid similar to that of the blood. It is however possible, as Schade points out, that in certain inflammatory processes acid may be produced in somewhat larger quantity, and this may perhaps increase the intensity of an edema which was primarily caused by other factors.

Only if a large amount of cellular material were breaking down very rapidly, such as occurs in the case of purulent inflammation, could enough acid be produced to become possibly a factor in the production of a localized edema, but this would constitute an extreme and strictly localized condition which would not be of significance as far as the analysis of edema in general is concerned.

Thus theoretical considerations and the actual determination of the hydrogen ion concentration lead both to the same conclusion; but in addition experimental and clinical facts give to it additional support. We may briefly mention some of these observations: (*a*) In experiments in which he produced edema in Trendelenburg preparations of frogs, through perfusion of salt solutions, Gayda found that

the addition of alkali to the perfusion fluid did not prevent the occurrence of edema. (*b*) The oral administration of considerable amounts of acid and alkali extending over a longer period of time, which according to Henriques and Ege may change the hydrogen ion concentration of the body fluids within relatively wide ranges, does not seem to lead to the production of edema. (*c*) In diabetes where the hydrogen ion concentration changes towards the acid side to a much greater extent than in many cases of renal or cardiac affections, which latter are often followed by edema, an edematous condition does not usually occur. On the contrary; diabetic individuals very often show a deficit of water, a condition which has been attributed by some authors to the increase of sugar in the blood of these patients. It is, however, possible to produce in diabetes, as well as in cases of inanition, extensive edemas through the injection of large quantities of sodium bicarbonate solutions. These edemas are possibly due to the introduction not of the hydroxyl but of the sodium ions and would thus be another instance of the effect of sodium chloride in the production of edema. We have discussed this kind of edema in a preceding chapter. (*d*) It has been shown by Schade that acid causes a swelling of the connective tissue fibrils, while alkali on the contrary causes a swelling of the colloidal material, which is supposed to fill the interfibrillar spaces. Now in typical cases of edema, the interfibrillar spaces are the seat of the swelling rather than the fibrils proper. This would be in agreement with the slightly alkaline character of the body fluids, which would become still further removed from the isoelectric point through the addition of alkali and consequently would bind a larger quantity of water. It must, however, be conceded that there is no certainty as to the existence of an amorphous colloidal ground substance, filling the interfibrillar spaces, which Schade and others assume. The presence of such a substance in a somewhat modified form is also assumed by Laguesse. This author maintains that the loose connective tissue consists of a system of lamellae formed by colloidal material in which are embedded the connective tissue fibrils. Connective tissue cells line these lamellar structures and these cells are also found in the interior of the lamellae. The latter can glide over each other. According to Laguesse these interlamellar spaces may serve as water reservoirs, if an excess of

fluid is eliminated from the vessels. In addition an imbibition of the colloidal ground substance would occur in edema. On the other hand Nageotte maintains that the lamellae of Laguesse are merely systems of fibrillar nets in which the fibrillae are closely approximated to each other. Spaces which intercommunicate with each other separate the fibrillae in case of edema. A homogeneous gelatinous substance, in which the fibrils are embedded, does not therefore exist, according to Nageotte. It is very probable that the latter view is the correct one and that in edema the fluid, with which is mixed a certain amount of colloidal protein material, separates these fibrils. (*e*) According to Bauer, acid instead of causing a swelling of nerve substance, on the contrary produces a dehydration of this tissue and acid cannot therefore be the cause of edema of the brain substance proper. (*f*) There are apparently some conditions where lack of oxidation processes and subsequently acid production or direct formation of acid may lead to localized edema within the cells of certain organs. Such changes have been described by Martin, Loevenhart and Bunting in tissues exposed to oxygen deficiency and by E. A. Graham in the liver of dogs under the influence of chloroform poisoning. Now, from our point of view it is of interest that in these cases a typical edematous condition of the interstitial tissue did not develop. (*g*) According to Fischer inflammatory edema depends upon the absorption of water by the colloids of the tissue which has been injured through the inflammatory alteration. Contrary to this view, Hirschfelder has shown that the conjunctivitis and chemosis of the lid which usually follow the instillation of mustard oil into the conjunctival sac of the rabbit, do not occur, if the lid is excised within three to four minutes following the instillation, at a time when the edema has not yet begun to develop. If the lid is next placed in Ringer's solution or in rabbit serum, it does not become edematous. Hirschfelder concludes therefore that the circulation is necessary for the development of this edema, but the circulation does take place through vessels in which the state of contraction and the permeability have been altered. (*h*) As Wallace and Pellini have pointed out, a number of substances which produce functional or structural changes in the blood-vessels call forth at the same time a state of acidosis. Now, from our point of view it is important that no relation

exists between this acidosis and the edema producing power of these substances.

3. M. H. Fischer assumes that, as far as their permeability for water and dissolved substances is concerned, cells and tissues are comparable to pieces of gelatin or fibrin; this author denies therefore that there exists a protoplasmic cell membrane, with a distinctive physico-chemical behavior and function and with a permeability for water and salts which may differ from that of the colloids which make up the contents of the cells. Contrary to this view, the studies of many investigators, like Hoeber, Jacques Loeb, Bethe, R. S. Lillie, Osterhout and others, have brought to light many facts which can hardly be explained otherwise than by the conclusion that a distinctive protoplasmic cell membrane separates cells and surrounding tissue fluid. The recent studies of Embden and his collaborators furnish additional evidence in favor of the existence around muscle of a protoplasmic membrane, possessing a distinctive permeability, which varies under different conditions.

4. One of the most important facts in the interpretation of certain experimental edemas is the rôle which sodium chloride retention plays in determining the intensity and duration of the edema. As we have seen, all evidence points to the conclusion that it is the sodium rather than the chlorine ion which is responsible for this effect and that other kations do not have an effect comparable to sodium. On the contrary the administration of potassium and calcium may lead to the elimination of the edematous fluid. This specific effect of sodium is not restricted to edema of renal origin, but may appear in other kinds of edema as well, and a theory of edema can therefore not disregard the connection between salts and edema.

Now it is important to note that the effects of sodium chloride in edema do not show any parallelism with the action of this salt on proteins; sodium chloride tends to diminish the swelling of gelatin under the influence of acid and alkali, while it increases the intensity of edema, or may cause edema as we have seen above. On the strength of the action of this salt on proteins, M. H. Fischer recommends hypertonic solutions of sodium chloride in the treatment of edema and particularly of glaucoma. The results of this mode of treatment do not seem to have been generally favorable, and when hypertonic salt

solutions have a beneficial effect on localized edema, it is due to their osmotic action and not to their effect in counteracting the influence of acid and alkali on proteins; otherwise isotonic solutions of this salt should prove effective in the treatment of edema; but this is not the case. In particular, this mode of treatment has not been found successful in glaucoma, according to the experience of the majority of ophthalmologists. Such a result was to be expected, if we consider that glaucoma is not due to an increased hydration of the tissues constituting the eyeball; and even if this were so, it would be difficult to understand why the relatively very small quantities of hypertonic salt solution, recommended by Fischer in the treatment of glaucoma, should be able to overcome successfully the affinity for water on the part of the colloids of the eye. The same discrepancy between the effects of salts in edema and their effect if acting directly on colloids was observed by Heubner in his study of the action of salts on the ligamentum nuchae in cattle. Quite recently Fischer offered a new explanation of the effects of sodium salts in edema in which he concedes the effect of this salt in increasing edema; but again his explanation is based on the assumption that edema consists primarily and essentially of an entrance of water into the parenchyma of organs and that the water is therefore mainly intracellular in character; for this and other reasons his hypothesis is not convincing.

As to the different degrees of effectiveness in the dehydrating action of various salts on colloids, we have in a preceding chapter referred to investigations showing that the citrate, tartrate, phosphate and acetate ions, which, according to Hofmeister and Fischer, exert a specific dehydrating effect on proteins, influence primarily the hydrogen ion concentration of the solutions and that therefore a specificity in the action of these ions does not really exist.

W. Hülse who, like Fischer, assumes that the primary seat of edema is the parenchyma of organs, recognizes the difficulties attaching to the hypothesis which attributes to the effect of acids the major rôle in the development of edema, and he therefore states that salts or other molecules combining with the colloids, cause their hydration. This author however gives no definite facts in support of his contention and he does not thereby account for the difference in the action of sodium and potassium salts in edema.

If we take into consideration all these facts, we may conclude that there is no reason to accept the view that edema consists in a hydration of the colloids in the parenchyma of organs caused by the influence of acids.

XVIII. THE MAIN FACTORS IN THE DEVELOPMENT OF EDEMA

In this concluding chapter we shall recapitulate some of the more general points of view we have arrived at, and we shall consider the relative importance of the various factors which we have discussed in the previous chapters. Such a discussion must necessarily be of a tentative character and it will at the same time serve to show the defects in our knowledge and the apparent or real contradictions in certain of the observations, clinical and experimental, and in some of the conclusions arrived at by different investigators.

The problem of edema

The factors which regulate the exchange of fluid and dissolved substances between blood and lymph vessels on the one hand, and the surrounding tissue spaces and serous cavities on the other, and again between the latter and the organs are complex and to this complexity corresponds the complexity of the factors which lead to a disturbance of this mechanism. While heretofore it has been customary to consider edema as a chapter in the pathology of lymph formation, we have considered it in a more general way as an interference with the mechanism which regulates the distribution of water and of dissolved substances in so far as the latter influence the distribution of water in the organism, and in particular as an interference with the mechanism which tends to keep in the first place the constitution of the blood and secondarily also the fluid of the tissue spaces constant. These interfering factors may be of a general or of a local character.

A complete understanding of edema would therefore presuppose a complete analysis of the factors which determine the normal movements of fluid and dissolved substances, also of the forces which regulate the absorption of fluid in the intestines, its excretion through kidney and elsewhere, and which regulate the permeability of capillaries and the constituent elements of organs. We would have to

know the influence of the mechanical factors concerned in the pumping of blood through the vessels on the movement of water outside the vessels, as well as the influence of various substances originating in the body on this movement. At present we can only indicate where a deviation from the normal factors sets in. Our main difficulty concerns the sequences to these initial disturbances. These we understand as yet only incompletely.

Correlated movements of fluid

We have seen that there is reason for the conclusion that under normal conditions the principal factors which determine the movement of water and dissolved substances and which regulate this mechanism form one connected whole, in which a disturbance in one part causes a regulatory disturbance at another point of the mechanism. Likewise in general edema similar connected mechanisms come into play, inasmuch as, for instance, an interference with the elimination of fluid and dissolved substances may cause changes throughout the body and lead to an overflow into the tissue spaces, while conversely this condition is remedied as soon as the primary disturbing factor is removed. We have found a number of instances in which not only this connection between different parts of the mechanism was clearly recognizable, but in which moreover the forces at work could be determined. Thus it was quite evident that the effect of adrenalin on elimination of fluid through the kidney influenced absorption from the peritoneal cavity, and that osmotic and diffusion potentials transmitted the effect from one part of the body to another part. In a similar manner, if under the influence of caffeine more water and salt pass from the blood into the kidney, the movement of these substances is correspondingly influenced throughout the organism at various points of the circuit. When we cause a deficiency or an excess in the intake or elimination of sodium chloride, a correlated movement of salt and water from tissue to blood, kidney or in the opposite direction follows. In the experiments of Magnus the excess of salt caused by the intravenous injection of a solution of sodium chloride is temporarily stored in the tissues and then given off by tissues to blood and kidney. Osmotic and diffusion differentials apparently regulate this movement. The amount of water and sodium

chloride deposited in the tissues has a marked effect on the elimination of water and salt through the kidney. There is a correlation of the exchange of fluid between tissue and blood on the one hand, and between blood and kidney on the other hand. The blood represents a station of transit, which is usually only temporarily disturbed, because it possesses outlets in both directions and thus a compensation can be more readily brought about. Under pathological conditions the amount of sodium chloride and water may vary also in the blood; during the period of discharge of the edematous fluid the concentration of sodium chloride in the blood may be temporarily increased. If diuresis takes place in cardiac edema, a dilution of the blood occurs at first and subsequently an increased concentration. In case of edema we find the movement of water changed in both directions in a correlated manner; while there is an inhibition of the movement from the tissues to the blood. In nephritis the drinking of much water may lead to an excess elimination of water into the tissues owing to the insufficient elimination through the kidney, and this is perhaps correlated with changes at the tissue-blood-vessel border. We have reason for assuming that this connected movement depends to a great extent on osmotic and diffusion potentials which may be, as the experiments of Priestly suggest, so small that they represent osmotic and diffusion differentials, and if we consider the changes in the permeability of blood-vessels which evidently occur in response to primary alterations in blood and tissues, there is reason for assuming that these changes also may play a part in this correlation.

Excess and pendulum reactions

This interconnection of mechanisms may lead to excess or pendulum reactions: a temporary excess of substances in one part of the interconnected system is created, which is equilibrized soon afterwards. Two such pendulum phases may even occur in succession. Thus in nephritis the drinking of much water may lead to an excess elimination into the tissue and to a temporary increased concentration of the blood. If in cases of acute glomerulonephritis or hunger edema at the time of the discharge of the edematous fluid a surplus of sodium chloride is taken in, more sodium chloride may be excreted than has been added to the diet. The addition of sodium chloride may mo-

bilize the stored up salt, which evidently is very loosely bound to the tissues. In cases of cardiac decompensation, after a dry retention of sodium chloride has taken place, an excess of the salt may be given off. In a similar manner drinking of water may cause an excess diuresis, more water being eliminated than had previously been taken up, if the water had been stored in the body without a proportionate amount of sodium chloride having been retained. Thus during the discharge of the edematous fluid an excess elimination of water may occur and this may lead to a temporary inspissation of the blood.

We find then, for instance, in hunger or renal edema, during the time of the discharge of the edematous fluid a process taking place similar to that seen under normal conditions, where drinking of water tends to mobilize a mechanism, which leads to a movement of water from blood or tissue to kidney, and which more than compensates for the intake. In edema this occurs as soon as the primary disturbance has been removed and the mechanism has been released which permits water and sodium chloride to move from tissue to blood or kidney.

Such excess reactions may also take place in cases of pre-edema when the mechanism of water and salt movements is not yet fully disturbed; here copious water drinking may set to work the opposite mechanism leading to an excess elimination of water through the kidney. The fact that such mechanisms exist not only in renal edema but also in hunger edema, when apparently the kidney functions well, suggests that there are mechanisms which regulate the movement of sodium chloride and water from the blood to the tissue and vice versa, independently of the kidney function and that the reëstablishment of the mechanism, which sets free the movement from tissue to blood, may stimulate the kidney to action, provided the renal function is satisfactory. A double regulatory mechanism thus exists: (1) A disturbance of one part of the connected mechanism leads to a compensatory reaction in the other part, and (2) A localized regulation, principally of a chemical, but secondarily also of a mechanical nature, occurs at the various boundaries.

We see then that the mechanism regulating the water and sodium chloride movement and content of the organism is a very delicate one; the lability of this mechanism is so great that a temporary excess

of water or salt in one part of the body may lead to a greater elimination of water and salt than the amount taken in and an excess reaction is brought about. Thus under certain conditions the movement of water and sodium chloride resembles reactions which take place under the influence of a stimulus, no simple quantitative proportion existing between stimulus and reaction. And this fact suggests the participation of sensitive tissues in these reactions, such as a variable permeability of capillary walls, which finely adjusts itself to various conditions.

Reversal of the movement of water and sodium chloride

In edema there are at work factors which change the current of water and sodium chloride in such a manner that a movement of these substances towards the tissue spaces and serous cavities is facilitated and the opposite movement from the tissue to blood and kidney is impeded. Such a change in the direction of the movement can be shown to exist in experimental uranium nitrate poisoning.

We have shown that such a reversal can be experimentally produced or accelerated through administration of caffeine in nephrectomized animals. A similar effect can be obtained in diabetes insipidus through administration of pituitrin. If this reversal continues for a sufficient length of time with sufficient energy, and if enough water is given, edematous or at least pre-edematous conditions can thus be experimentally produced. It is probable that osmotic and diffusion potentials are active in this reversal of current. Differences of concentration may perhaps be associated with changes in the permeability of membranes, which may lead to changes in the concentration of various substances on both sides of the membranes. We know that pituitrin may affect the permeability of membranes, decreasing the permeability of the capillaries.

The action of thyroid resembles the effects of pituitrin and caffeine in so far as all of these substances act on the intermediate water and sodium chloride movement; but while caffeine and pituitrin under the conditions we mentioned increase and accelerate the movement towards the tissues, thyroid accelerates the movement in the opposite direction. We see then that certain substances may affect the intermediate current of water and sodium chloride in a specific manner

leading either to a pre-edematous condition or to the opposite effect, the discharge of the edematous fluid. Whenever the normal current of water tending to excretion is interfered with, a reverse current towards the tissues tends to occur, similar to that accelerated by caffeine after extirpation of the kidney. Caffeine and similar substances, which under normal conditions hasten the elimination of sodium chloride and water, and in an edematous state may induce the discharge of the edematous fluid, provided the kidney is sufficient for this purpose, may otherwise not only be without effect, but may, as we have seen, even favor the opposite movement, namely, that towards the tissues.

There are some indications that the movement of sodium chloride in one direction may be equalized by a movement of other substances in other directions, and that thus an equalization in osmotic pressure may be brought about.

Edema as a compensatory process

Under various pathological conditions mechanisms exist which tend to keep the composition of the blood as constant as possible. It has, for instance, been shown that there is a mechanism which in this sense takes care of the hydrogen ion concentration of the blood, substances which threaten a marked alteration being soon eliminated. In this way the circulating medium, which keeps up the exchange of substances between the various parts of the organism, an exchange leading to the elimination of the waste products, is enabled to function at the expense of parts in the organism which are less essential for the organism as a whole. There is also a mechanism which keeps the water content and the concentration of various substances in the blood constant. Two main outlets exist for material which might lead to pathological alterations in the blood, namely, the tissues and the kidneys. There seem to be special reservoirs which, in the normal organism, principally take care of a surplus of water or sodium chloride, the muscle in the case of the former and the skin in the case of the latter. After a temporary storage, the surplus is eliminated chiefly through the kidney. If the disturbance connected with the retention of these substances is greater, they are eliminated mainly into the subcutaneous tissue and into the serous cavities and are kept there

until the disturbance in the primary mechanism, has been removed. Thus again the constitution of the circulating medium is kept constant, at least within certain limits, although we have seen that temporary alterations due to excess and pendulum movements do occur; and if the alteration is furthergoing, certain changes in the blood may be of even longer duration. But the surplus tends to be eliminated into the tissues and to be kept there and thus edema is produced. In this sense we may consider edema as a compensatory process insuring relative safety to the organism.

It is of interest to inquire, why the blood has this advantage? It seems to be due to the fact mentioned above that the blood is surrounded on both sides by a mechanism which serves for elimination of water and dissolved substances, namely, the tissues and the kidney. It is this advantageous position of being in the center of this system which tends to insure the relative constancy in the composition of of the blood. In addition to representing a place of elimination, the tissue also is a supply room, from which substances may be taken up. As we have seen, there is a multiplicity of primary factors which regulates this constancy in the distribution and movement of water and salt in the body. They are connected with each other and to some extent a deficiency at one point can be compensated for through the regulating activity of another part. A last regulation occurs in the form of edema. If we inquire into the factors which serve the function of these primary mechanisms, the evidence points to the conclusion that changes in the permeability of membranes, and in particular of the capillaries and osmotic and diffusion potentials, are the principal instruments which come into play in the normal regulation of the constitution of the blood, as well as under those conditions which lead to edema.

Edema as a graded process

According to the definition, edema is a swelling due to the collection of fluid in certain parts of the body; this definition of edema would presuppose a discontinuous process. In reality all transitions seem to exist between the normal distribution of fluid on the one hand, and edema on the other, a state of pre-edema representing an intermediate stage between these two extreme conditions. The determinations of

Kauffman in heart disease indicate the existence of such intermediate stages under circumstances which ultimately lead to cardiac edema. The transitional stages are due not only to a continuity in intensities in the accumulation of fluid, but also to variations in duration which range from temporary disturbances, as those of shock, to long continued edema.

Multiplicity of factors in edema

We can distinguish three sets of factors which regulate the normal movement of water and dissolved substances. (1) The primary factors represent, as we have seen, a more or less connected mechanism, which includes the absorption, circulation and elimination of fluid. (2) The secondary factors include diffusion and osmotic potentials and perhaps endelectrosmotic forces, changes in the permeability of membranes, and probably to a limited extent filtration pressure. (3) We can, if we proceed still further in our analysis, recognize a third class of factors, comprising the means through which the second set of factors exert their effect. These would include the distribution of sodium chloride and of proteins, both of which are of special importance in establishing and regulating osmotic and diffusion potentials; in addition the protein aggregates may retain water in a specific manner. The third class would also include those factors which regulate the permeability of membranes,—as for instance, a certain equilibrium of ions,—the action of certain hormones and other conditions. Now all of these factors which are of significance in the normal movement and distribuiton of fluid must necessarily also be factors in the development of edema; but there is discernible besides in a number of cases a multiplicity of those factors which deviate from the normal to such an extent that edema results. Some of the better known instances are the following: Hydremia as such does not cause general anasarca in the rabbit; but if in addition effects are added, which in all probability increase the permeability of the capillaries, as for instance, those following the administration of iodine or arsenic, and those following the death of the capillaries, then general edema follows. While venous obstruction alone may not cause edema in many cases, combined with hydremia or with arterial hyperemia, it may produce this effect. In a similar manner venous obstruction

accompanied by the injection of hypertonic salt solution may cause edema. Administration of amylnitrite may cause edema in chromate rabbits, and it may increase it in uranium nitrate nephritis; presumably this substance leads to a slowing of the circulation and thus to an increase in the permeability of the vessels. In the embryo, after elimination of the kidney function, injury to the vessels of the skin in the area surrounding the place of incision, causes edema to appear at this point, while elsewhere cutaneous edema is lacking.

There are indications that a similar multiplicity of factors comes into play in clinical forms of edema. Thus in edema observed in undernourishment several factors may be responsible, as an increased deposition of sodium chloride in the tissues, hydremic blood, and a consequent decrease in the power of the blood to retain and attract water, and perhaps an increased permeability of the vessels and a weakened circulation. In nephritis possibly the effect of substances given off by the diseased kidney, or of substances causing simultaneously pathological changes in kidney and blood-vessels, may be added to effects due to the retention of substances normally eliminated through the kidney, which latter may set up osmotic and diffusion potentials and influence the membrane permeability. In cardiac decompensation there is a slowing of the circulation which is associated with a dilatation and presumably an increased permeability of the capillary vessels; but an increased filtration pressure may perhaps exert an additional influence in certain cases. Similarly in lymphatic edema there may be added to the mechanical factors changes in the permeability of the vessels and in osmotic potentials. As we have seen multiple factors may even be present, when one factor seems to play a predominant rôle, as, for instance, in inflammatory edema, where the increase in the permeability of vessels is the most striking feature. In this case an increase in osmotic pressure and in the colloid content of the affected area may also play a part. But, while there is a multiplicity of factors which come into play, this does not exclude the probability that these various factors differ greatly among themselves in importance and that a few factors play a predominant rôle in edema. We shall therefore discuss separately some of the factors of the second and third class from this point of view.

The rôle of sodium chloride in edema

In the normal organism sodium chloride plays an important rôle in causing the retention of water in the body as a whole and in the fixation of water in certain tissues or organs. With a deficit of sodium chloride in the organism water is eliminated in an otherwise normal person. When a tissue is made poor in salt, water leaves the tissue. When there is lack of sodium chloride in the body, a lack of water cannot be made up very readily. On the other hand, a surplus of salt given with the diet leads to the retention of water. In the normal person the retention of water in the body is apparently, to a great extent, an osmotic phenomenon. We have reason to assume that sodium chloride plays a similar rôle in edema; only in edema a certain primary mechanism is disturbed and as a result of this alteration irregular distributions of sodium chloride take place apparently on a much larger scale than in the normal person, and the movement of water follows that of the sodium chloride. We know that a surplus of sodium chloride has a special tendency to be deposited in the skin and correspondingly here edema develops preferably. In general under normal, as well as under pathological, conditions a surplus of sodium chloride tends to be retained in the blood only for a short time, and if possible it is moved either to the kidney or deposited in the tissues; this latter process leads to edema; in certain cases, however this mechanism is interfered with and the salt may be retained for a longer period of time in the blood. Slight differences in the concentration of sodium chloride or water on both sides of permeable membranes lead to movements which tend to reëstablish the normal equilibrium. This equilibrium is a very labile one especially in normal persons as well as in persons who are ready to discharge their edema; a slight surplus of water or salt may lead to excess reactions.

With these views agree the many data concerning the movement and distribution of sodium chloride in renal insufficiency; we know likewise that in cardiac decompensation and in states of undernourishment there tends to be a retention of this salt. In pneumonia sodium chloride seems to accumulate in the lungs, and it is possible that also in other inflammatory foci a local retention of this salt occurs and that this fact contributes to the production of inflammatory edema.

While many researches concurrently indicate the great significance of sodium chloride in edema, it is necessary to point out that the majority of investigators made determinations merely of chlorine and not of sodium; the recent work of R. F. Loeb, Atcheley and Palmer has however shown that the distribution of these two constituents does not necessarily follow a parallel course. These investigators found an equal concentration of sodium in blood and edematous fluid; but in their cases endpoints in the equilibrium had probably been reached and these may have been preceded by an unequal distribution of sodium chloride between the blood and the tissue.

The rôle of proteins in edema

In certain respects similar to the rôle of sodium chloride is the part which proteins play in edema and in the distribution of water in general. Neither changes in the distribution of the sodium chloride, nor of the proteins play a primary part in the origin of edema; but both are concerned in the movement and distribution of water. We have found many instances in which proteins or other colloids influence the distribution of water. There are, however, also important differences between the sodium chloride on the one hand and the proteins on the other. It has not been possible to find any definite indications that changes in the concentration or character of the proteins determine the development of edema in a way comparable to the effect exerted by sodium chloride, and the amount of edematous fluid does not correspond to the protein content of the blood. We have found a marked independence in the development and discharge of edematous fluids of their content in proteins. We have seen that the effect of various substances on the water binding power of colloids, which Ellinger observed, does not correspond to the effect of these substances on edema.

While it does not therefore appear probable that the edematous retention of water in the tissue spaces depends mainly on the amount of protein which can pass through the capillary walls, owing to the increased permeability of the latter, still this protein must necessarily cause some retention of water and thus the protein must play at least a subsidiary rôle in the development of edema. It is therefore likely that the views of Eppinger, which are also sustained by the

experiments of Ellinger, hold good only in a restricted sense. At present we must however admit the possibility that future investigations may necessitate a modification of this conclusion, and it is especially the experiment of Morawitz and Deneke on the swelling of gelatin in uranium nitrate animals which, if substantiated, might perhaps point to a higher valuation of the significance of the interstitial proteins in edema. On the other hand, the views of M. H. Fischer as to the significance of organ colloids in the origin of edema, are not in harmony with the observed facts. This is true also of views of Hülse which, as far as we are aware, do not find any support in the known facts of the chemistry of proteins.

In particular as far as the views of Fischer concerning the effect of acid substances in edema are concerned, we have seen that, inasmuch as a part of the proteins exist in the body fluids as sodium proteinates, an increase in hydrogen ion concentration would tend to diminish rather than add to the water binding power of the proteins; on the other hand, the effect of an increased alkalinity might conceivably make more pronounced in a direct manner their water binding power.

Osmotic and diffusion potentials in edema

Osmotic and diffusion potentials help to regulate the exchange of water and salts between tissues or serous cavities and the blood and lymph. The experiments of Hamburger on the exchange between peritoneal cavity and blood, as well as those of Magnus on the distribution of hypertonic solutions of sodium chloride after intravenous injection, have proven the influence of osmotic and diffusion potentials in equalizing differences in concentration which originate in the body. We have learned in addition that various abnormal conditions may lead to localized alterations in the osmotic pressure within the organism. Thus we could show that following operations in general (Fleisher and Loeb) as well as after nephrectomy (Meltzer and Salant) the movement of water from the peritoneal cavity to the blood is accelerated in accordance with changes in osmotic pressure, which have been produced. We furthermore noticed that caffeine and adrenalin exert their effect on the movement of water and salt in accordance with osmotic changes which they call forth. In agreement with the observations of various investigators, we may conclude in

general that whenever edema tends to develop a retention of sodium chloride in the tissues is apt to have preceded this condition and thus presumably osmotic and diffusion potentials have tended to arise. As Priestly has made probable in the case of the diuretic effects of sodium chloride, very small differences in concentration of this salt may call forth movements of fluid leading to the elimination of water. Whenever sodium chloride is not sufficiently excreted, it tends, as we have seen, to accumulate in the tissue spaces rather than in the blood. It is significant that it is the distribution of the sodium ion more than that of any other substance which has a positive effect on the development of edema. This may be due to the fact that sodium can accumulate in the tissue spaces in a much greater quantity than any other ion and that at the same time it cannot readily penetrate into the cells or tissues proper; thus it accumulates in places where later edema develops, and presumably it is at least in part responsible for the movement of water into the tissues and for its retention in the tissue spaces. While thus differences in concentration are equalized, at the same time membrane equilibria, comparable to the Donnan equilibrium, become effective and lead to an unequal distribution of the sodium and chlorine ions.

It is of interest that some of the substances, which thus directly or indirectly create osmotic or diffusion potentials, tend also to alter the permeability of membranes; for instance, a changed equilibrium between sodium, potassium and calcium ions in the blood produces this result and in uranium poisoning the effect of substances like adrenalin and caffeine on the movement of water is lost perhaps on account of the alteration produced in the permeability of the membranes by uranium nitrate. It might be suggested that changes in membrane permeability may in some way affect the movements of salt and contribute to the creation of differences in concentration which lead to edema. The reversal of the current of fluid towards the tissue, which can be produced experimentally through the administration of caffeine in nephrectomized animals, or through the administration of pituitrin in diabetes insipidus, is also presumably the result of changes in concentration within the tissues; in this case also changes in permeability may possibly coöperate. Likewise the fact that in edema there is not only an increased current of fluid

towards the tissues, but also an inhibition of the reverse movement of fluid or salt from the tissues to the blood, suggests the activity of differences in concentration in causing a retention of fluid within the tissue spaces. We believe that the evidence which we have at the present time favors the conclusion that differences in the concentration of various substances in blood and tissue are at least partly responsible for the development of edema.

Localized edema

In many respects localized edema, and in particular inflammatory edema, is more favorable for the analysis of factors which cause edema than generalized edema. It is especially in localized edema that the great significance of changes in the permeability of the capillaries in edema was clearly established. Cohnheim and Lichtheim, as well as Starling, drew attention to local differences in the permeability of capillaries; furthermore there are local differences in the tissue pressure and local differences in the eliminating action of certain glands, like the salivary glands, which have likewise to be considered.

Inflammatory edema might almost be considered as due to the boring of holes through a dam, in consequence of which a local overflow of fluid occurs. In reality, however, such an increase in permeability is of a more complex character; it is graded and selective. Yet even in inflammatory edema other factors besides an increase in the permeability of capillaries probably come into play. Recent investigations have contributed much to the understanding of the factors which influence the permeability of capillaries and we are beginning to appreciate the complexity of these factors. A certain balance of ions influences the permeability of capillaries; potassium in particular seems to increase and calcium to decrease it; but under certain conditions an increase in the quantity of calcium may apparently lead to the opposite effect. The influence of potassium on the permeability of capillaries has a special interest in view of the fact that it has recently been found that the potassium content of the blood plasma is relatively increased in cases of edema. In addition carbon dioxide tension and hydrogen ion concentration, oxygen tension and certain hormones, like pituitrin and adrenalin, affect the permeability. All or the majority of these factors probably coöperate in regulating the

state of the capillaries. In general, it seems that a contraction of the capillaries is associated with a decrease, and a dilatation with an increase in permeability. In this connection it is of interest that we found indications of a similar condition in the case of the membrane of individual cells like the amebocytes. Chemical stimulation leads on the whole to a dilatation and to an increased permeability of the capillaries; this mechanism would therefore be favorable to an elimination of a strange substance. While thus much progress has been made in the analysis of the capillary permeability, some of the problems relating to inflammatory edema are not yet clearly understood. In particular the evidence as to the mechanism determining inflammatory dilatation of the capillaries and increased transudation is as yet somewhat contradictory.

While it is of great importance to study the localized behavior of capillaries, we must not forget that in the organism as a whole other factors besides the state of the capillaries have to be considered in the development of edema, and that the same substance may affect different mechanisms in a different manner; only in this way can we understand certain apparent contradictions in the evidence which we find in the literature. Thus we have seen that calcium affects the elimination of fluid through the interstitial wall, through the kidney and through the peritoneal lining each in a specific manner. In addition it has a specific effect on the heart action. Thus while calcium may under certain conditions prevent inflammatory edema, it may on the contrary increase the amount of peritoneal transudate; while usually it decreases urinary secretion, it may in certain cases accelerate the discharge of edematous fluid through the kidney.

Edema and the permeability of membranes

There are reasons for assuming that changes in the permeability of the capillaries play a considerable rôle not only in localized edema but in all kinds of edema. Yet if we consider critically the facts learned so far, our knowledge in this respect appears rather scant. We can be certain that changes in permeability play a great part in localized and in particular in inflammatory edema. In other cases there is also experimental evidence which renders it at least probable that factors which increase the permeability of vessels cause or contribute

to the development of edema. Reference may be made to the action of iodine, arsenic and chloroform, heat, of hematoporphyrine in combination with sunlight, of aromatic, fat soluble amins and other similar effects. We have seen that certain substances like thyroid, adrenalin, and calcium which have specific effects on the movement of water and dissolved salts, likewise affect the membranes of cells or tissues in a specific manner. Whether caffeine has a similar effect, seems uncertain at the present time. In general we have learned of the great variability in the permeability of cell membranes and the relation of these variations to functional changes in the cells. It is of interest in this connection that on the whole cells seem to be little permeable to fluids analogous to edematous fluid and this may be one of the factors which is responsible for the location of edema in the interstitial spaces rather than in the tissues proper.

It is natural that under those conditions we should be inclined to generalize as to the significance of an increase in the permeability of vessels. Yet we must confess that the evidence we have in the majority of cases of clinical edema, as to the significance of changes in the permeability of vessels, is either circumstantial or even contradictory. Thus in uranium nephritis earlier findings, indicating a more rapid elimination of sodium chloride solution through the capillaries, were not confirmed by later investigators, who, on the contrary, found a retardation; still it is possible that osmotic factors are implicated in the latter result. But we also found the movement of water and sodium chloride from the peritoneal cavity to the blood-vessels retarded and the specific effects of caffeine and adrenalin no longer clearly in evidence in uranium nitrate poisoning. On the other hand, Krogh and Harrop found a local increase in the permeability of the capillaries under the influence of uranium nitrate; and we may also refer to the observations of Morawitz and of Donner which indicate an increase in the vascular permeability in certain kinds of nephritis. In cardiac decompensation, the evidence again is circumstantial; we assume that the dilatation of the capillaries combined with an increase in carbon dioxide tension in the capillary blood may increase the permeability. Similarly circumstantial is the evidence in the case of hunger edema. In this state of our knowledge, it is difficult to give a positive answer to the question, whether edema

is primarily due to changes in the kidney, or in the tissues, or whether both factors are equally involved. The question may also be put in this way: Is the increase in the permeability of the vessels which communicate with the tissues dependent on an insufficiency of the kidney and subsequent retention of substances, or is it a primary factor independent of the kidney function. We have seen that we cannot answer this question with certainty; but we consider it probable that both a retention of substances and a change in the capillary permeability play a part.

As to the variables which determine the movement of fluid through membranes and especially through capillaries in the living organism, we have to consider (1) osmotic and diffusion potentials and the specific effects of proteins; (2) electrostatic forces, electro-endosmosis, abnormal osmosis; but of the action of these in the development of edema, we are ignorant at present; (3) capillary forces, (4) factors depending upon the state of contraction of the living units which compose the membranes. As already stated in general a state of contraction decreases the permeability and dilatation tends to have the opposite effect.

Hydremia and edema

We have seen that injections of large amounts of an isotonic sodium chloride solution leads to the formation of transudates in the serous cavities and to the collection of fluid in the interstitial tissue spaces in certain areas, but not generally in the subcutaneous tissue. In this case we have to deal both with a hydremic change in the composition of the circulating blood, as well as with an increase in the quantity of the fluid, with therefore a polyemia. These factors then in themselves are not sufficient to cause typical subcutaneous edema.

Under a variety of conditions there may be in the blood, according to a number of investigators, a hydremia and polyemia or on the contrary an inspissation of the blood. These conditions are usually diagnosed by following the variations in the refractive index of the blood plasma, which indicates the amount of protein in the plasma, or by following the variations in the number of erythrocytes. Neither of these methods can give absolute values for quantity of blood or plasma; but so far as the quantity of protein is concerned, it seems to

be a much more variable factor than the erythrocyte count, especially since it has become known that proteid may enter and leave the blood-vessels under various pathological or experimental conditions. We may attach a comparative value to successive determinations of the variations in the number of erythrocytes. From all the investigation it follows that there is no direct relation between the state of dilution or inspissation of the blood and the development of edema. However, in hydremia there may be a subsidiary factor which, especially in association with other factors, may favor the production of edema.

Blood pressure and edema

Blood pressure as such is a factor in the development of edema; we have seen that a lowering of the blood pressure below a certain point prevents the occurrence of inflammatory edema. There are some indications that an increased filtration pressure, due to a rise in blood pressure, may under certain conditions cause edema or at least be a contributory factor to it. Thus in edema of the lung a marked rise in blood pressure may in some cases be responsible for the pressing out of fluid into the interstitial tissue and into the alveoli of the lung. In the portal system also an obstruction to the outflow of venous blood and increased capillary pressure may lead to increased transudation and lymph formation (Starling, Manwaring), and it is possible that the effect of adrenalin on the peritoneal transudate may be due to an increase in filtration pressure in the portal area. But in the majority of cases we find no direct connection between a rise in blood pressure and the development of edema; this is especially noticeable in cases in which the rise in blood pressure is due to renal disease. Furthermore usually under conditions in which a rise in blood pressure is found, other changes are associated with the alteration in blood pressure and these associated changes may lead to an increased permeability of the vessels and thus to edema. Taking all these facts into consideration we may conclude that an increased filtration pressure can represent at best only a factor of minor importance in the origin of edema.

We find thus indications that a multiplicity of factors is responsible in a similar manner for the distribution and movement of fluid in the normal organism and under pathological conditions, but that the importance of the various factors in the origin of edema differs greatly.

Changes in the permeability of capillaries acting jointly with differences in the concentration especially of sodium chloride seem to be mainly responsible for the abnormal retention of fluid in the interstices of the tissue and in the serous cavities. An abnormal distribution of proteins may play a contributory rôle. Other factors which we named are of less importance; they may act either indirectly by influencing the first named factors, or directly under special conditions.

The last fifteen years have contributed much to the understanding of different types of edema; and the analysis of the movement of water and dissolved substances from one part of the organism to another, of the factors which regulate the permeability of the capillaries, and of the conditions which determine the power of colloids to attract water, has much increased our knowledge. New views have been opened through the discovery of substances which affect the movements of fluid in the organism in a specific manner. Yet, after all, our understanding of the interaction of those factors which determine the normal distribution and movement of water in the organism is still incomplete; and this is true also of the interaction of these factors in edema. Even our knowledge of the changes in the permeability of capillaries in edema is fragmentary and at present we cannot exclude the possibility that instead of the increase in permeability which has been definitely proven in certain cases there may not be in other cases on the contrary a decrease in permeability which would make it possible for changes in concentration of various substances to develop. There are certain fields, as for instance, the significance of electrostatic forces in the movement of water under pathological conditions, about which we are in ignorance at the present time; our understanding of the relations between proteins and water is likewise still incomplete in several respects. We can therefore regard all general conclusions as to the development of edema at the present time merely as tentative, and we must expect that additions to our knowledge in the near future will necessitate a revision of some of our present conceptions.

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